HEPATITIS B VIRUS INFECTION: A COMPREHENSIVE IMMUNIZATION STRATEGY TO ELIMINATE TRANSMISSION IN THE UNITED STATES

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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SUMMARY

This document updates the immunization strategy to eliminate hepatitis B virus (HBV) transmission in the United States, which was published in 1991 and expanded in 1995. The document also updates technical information on hepatitis B vaccination of infants, children, adolescents, and adults, including: 1) hepatitis B vaccine dosages, formulations, and schedules; 2) guidelines for vaccination of premature infants; 3) guidelines for serologic testing before and after vaccination; and 4) guidelines for postexposure management of persons exposed to blood that may contain HBV. In addition, guidelines for implementation of the immunization strategy to eliminate HBV transmission are provided.

This statement consolidates and updates previous recommendations on protection against HBV infection, including those on use of hepatitis B vaccine and hepatitis B immune globulin; routine testing of pregnant women and immunoprophylaxis of infants born to hepatitis B surface antigen-positive mothers to prevent perinatal HBV transmission; immunization of adolescents aged 11-12 years and children at increased risk of infection; expanded access to hepatitis B immunization for children and adolescents from birth through 18 years of age; use of combination vaccines containing a hepatitis B vaccine component; changes in hepatitis B vaccine formulations and schedules; and preference for administering the first dose of the hepatitis B vaccine series at birth.

INTRODUCTION

Hepatitis B virus (HBV) is a bloodborne and sexually transmitted virus. Rates of acute disease are highest among adults, but chronic infection is more likely to develop in persons infected as infants or young children. Immunization with hepatitis B vaccine is the most effective measure to prevent HBV infection and its consequences. During 1990-2002, the incidence of acute hepatitis B in the United States declined 67%. The most significant decline (89%) occurred among children and adolescents, coincident with an increase in hepatitis B vaccination coverage; during 1993-2002, coverage increased from 16% to 90% among children aged 19-35 months and from near 0 to 67% among adolescents aged 13-15 years. The incidence of acute hepatitis B declined at a much lower rate among adults, who accounted for the majority of cases, and incidence even increased among some adult age groups.

Although the clinical manifestations of acute hepatitis B can be severe, the most serious complications, such as cirrhosis and primary hepatocellular carcinoma (HCC), occur among persons who develop chronic infection. Chronically infected persons are also the primary source for HBV transmission to others. In the United States, 1.25 million persons in the general population and 36,000 incarcerated persons are estimated to have chronic HBV infection; an estimated 3,000-5,000 persons die each year from hepatitis B-related complications. Because the risk of developing chronic infection is inversely related to age, persons infected in early childhood suffer a disproportionately large burden of morbidity and mortality attributable to HBV.

This document outlines an updated strategy to eliminate transmission of HBV infection in the

United States by use of preexposure and postexposure hepatitis B immunization. The recommended groups for routine preexposure hepatitis B vaccination are 1) all infants, 2) previously unvaccinated children and adolescents <19 years old; and 3) adults in target groups, including persons with behavioral risks, persons with certain medical conditions, persons in certain occupational groups, and groups in institutional-, medical- , and custodial-care settings. The target groups for postexposure immunization are 1) infants born to HBV-infected mothers; 2) persons with occupational exposure to blood or body fluids that contain blood; 3) sexual and household contacts of persons with acute hepatitis B and chronic HBV infection; and 4) victims of sexual assault.

MAJOR CHANGES IN THE RECOMMENDATIONS

Major changes in the guidelines since 1995 include the addition of the following:

- Recommendations for implementation of policies and procedures in delivery hospitals to ensure prevention of perinatal HBV transmission, including standing orders for administration of hepatitis B vaccination as part of routine care of all medically stable infants weighing ≥2,000 grams at birth, unless there is a physician's order to defer vaccination
- Recommendations for maintenance of case-management programs to prevent perinatal HBV transmission
- Recommendations to promote vaccination of adults in target groups, including:
    - Offering vaccine to all unvaccinated adults when seen in sexually transmitted disease (STD) clinics, testing and counseling programs for persons with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome

(AIDS), clinics for treatment of persons with HIV infection, and substance abuse prevention, treatment, and harm-reduction clinics and programs

- Implementing programs to ensure high vaccine coverage for a) persons at occupational risk of exposure to blood or blood-contaminated body fluids; b) at-risk persons in institutional-, medical-, and custodial-care facilities (e.g., correctional facilities, dialysis facilities, institutions for the developmentally disabled); and c) susceptible household and sexual contacts of hepatitis B surface antigen (HBsAg)-positive persons
- Implementing targeted outreach programs to vaccinate at-risk persons who rarely visit traditional healthcare settings and public health programs
- Implementing immunization registries for adolescents and adults to track receipt of hepatitis B vaccine, with particular emphasis on persons who receive vaccine in multiple settings

- Recommendations for screening and vaccination of immigrants and international adoptees

BACKGROUND

Clinical Features and Natural History of Hepatitis B Virus Infection

HBV is a 42-nm DNA virus classified in the family hepadnavirus. The liver is the primary site of HBV replication. After exposure, the virus enters the liver via the bloodstream; there is no evidence for replication of the virus at mucosal surfaces. HBV infection can produce either asymptomatic or symptomatic infection. The average incubation period is 90 days (range: 60-

150 days) from exposure to onset of jaundice, 60 days (range: 40-90 days) from exposure to onset of abnormal serum alanine aminotransferase (ALT) levels, and 30 days (range: 6-60 days) from exposure to detection of HBsAg. Highly sensitive single-sample nucleic acid tests can detect HBV DNA 10-20 days before detection of HBsAg.

The onset of acute disease is usually insidious. Infants, young children (aged <10 years), and immunosuppressed adults with newly acquired HBV infection are typically asymptomatic. When present, clinical symptoms and signs might include anorexia, malaise, nausea, vomiting, abdominal pain, and jaundice. Extrahepatic manifestations of disease (e.g., skin rashes, arthralgias, arthritis) can also occur. The case-fatality rate from acute hepatitis B is 0.5%-1%.

Most (≥95%) primary infections in adults with normal immune status are self-limited, with elimination of virus from blood and development of lasting immunity to reinfection. In ≤5% of healthy older children and adults, 30% of children <5 years old, and 80%-90% of infants, primary infection develops into chronic infection, with continuing viral replication in the liver and persistent viremia. Primary infections also develop into chronic infections more frequently in immunosuppressed persons (e.g., hemodialysis patients; persons with HIV infection).

Although the consequences of acute hepatitis B can be severe, most of the serious sequelae associated with the disease occur in chronically infected persons. Persons with chronic infection also serve as the reservoir for continued HBV transmission. The natural course of chronic HBV infection varies by age at infection, geographic location, and hepatitis B e antigen (HBeAg) status. Most persons with chronic HBV infection who are HBeAg-negative have normal ALT levels and minimal or no necroinflammation on liver biopsy, although up to 20% of persons with

inactive disease can have exacerbations of hepatitis. In contrast, most chronically infected persons who are HBeAg-positive develop chronic liver disease. Based on data from follow-up studies of persons infected with HBV as infants or young children, approximately 15%-25% of those with chronic infection die prematurely from cirrhosis or liver cancer; most remain asymptomatic until development of cirrhosis or end-stage liver disease. Extrahepatic manifestations related to chronic HBV infection are immune complex-mediated diseases, including membranoproliferative glomerulonephritis. Among persons with chronic HBV infection, possible risk factors for developing liver disease include older age, male gender, presence of HBeAg, HBV genotype, mutations in the precore and core promoter regions of the viral genome, and coinfection with hepatitis D (delta) virus. Prognostic factors for the development of cirrhosis include HBeAg positivity, older age, and elevated ALT levels. An association between alcohol use and progression to HCC in persons with chronic hepatitis B has been reported in some studies but not in others; these discrepancies may be related to the accuracy of the alcohol history.

The role of chronic coinfection with HBV and other viruses in facilitating the progression of liver disease is not clear. Results of studies on the effect of concurrent infection with HBV and HIV or HBV and hepatitis C virus (HCV) on the natural history of chronic liver disease are inconsistent. The strongest evidence, provided by studies from Japan and Italy, points to a possible synergistic effect of HBV/HCV chronic infection on the risk of developing HCC. Except for a few case reports, no evidence suggests that persons with chronic liver disease are at increased risk for fulminant hepatitis B.

There is no treatment for acute hepatitis B. Persons with chronic HBV infection require medical

evaluation and regular monitoring. Three therapeutic agents have been approved by the Food and Drug Administration (FDA) for treatment of chronic hepatitis B: interferon alpha, lamivudine, and adefovir. The aims of treatment are to achieve sustained suppression of HBV replication and remission of liver disease. In general, less than half of patients treated achieve HBeAg seroconversion. The most important predictor of response is high pretreatment ALT levels.

Diagnosis of Hepatitis B Virus Infection

The antigen-antibody systems associated with HBV infection include HBsAg and anti-HBs, hepatitis B core antigen and anti-HBc, and HBeAg and antibody to HBeAg (anti-HBe). One or more of these serologic markers are present during different phases of HBV infection (**Table 1**). Serologic assays are commercially available for all of the markers except hepatitis B core antigen because no free hepatitis B core antigen circulates in blood.

The presence of HBsAg is indicative of ongoing HBV infection. All HBsAg-positive persons should be considered potentially infectious. In newly infected persons, HBsAg is the only serologic marker detected during the first 3-5 weeks after exposure, and it persists for variable periods. Transient HBsAg positivity (lasting <21 days) can be detected in some patients after vaccination. Anti-HBc develops in all HBV infections, appearing at the onset of symptoms or liver test abnormalities in acute HBV infection, rising rapidly to high levels, and persisting for life. Acute or recently acquired infection can be distinguished by the presence of the immunoglobulin M (IgM) class of anti-HBc, which is detected at the onset of acute hepatitis B

and persists for approximately 6 months if the disease resolves. In patients who develop chronic hepatitis B, IgM anti-HBc persists at low levels during viral replication. However, commercial assays for IgM anti-HBc generally detect this antibody only when it is present in high titers.

In persons who recover from HBV infection, HBsAg is eliminated from the blood, usually in 2–3 months, and anti-HBs develops during convalescence. The presence of anti-HBs generally indicates immunity from HBV infection. Most persons who recover from natural infection will be positive for both anti-HBs and anti-HBc, whereas persons who are successfully vaccinated against hepatitis B develop only anti-HBs. Naturally acquired isolated anti-HBs (i.e., anti-HBs alone) has also been reported in unvaccinated persons. Limited data indicate that in most (80%) persons with this pattern, the antibody level is low (<10 mIU/mL), does not persist, and is not protective. In persons who do not recover from HBV infection and who become chronically infected, HBsAg (and anti-HBc) persist, usually for life. Approximately 0.5% of chronically infected persons will clear HBsAg yearly; most will develop anti-HBs.

In some persons, the only HBV serologic marker detected is isolated anti-HBc. Among most asymptomatic persons in the United States tested for HBV infection, an average of 2% (range: <0.1%-6%) test positive for isolated anti-HBc; the rate is higher (24%), among injection-drug users. In general, the frequency of isolated anti-HBc relates directly to the frequency of previous HBV infection in the population. Isolated anti-HBc can develop after HBV infection among persons who have recovered but whose anti-HBs levels have waned or among persons who failed to develop anti-HBs. Persons in the latter category include those with circulating HBsAg levels not detectable by commercial assays. These persons are unlikely to be infectious except

under circumstances involving direct percutaneous exposure to large quantities of blood (e.g., blood transfusion); HBV DNA has been detected in <10% of persons with isolated anti-HBc. For most persons in whom isolated anti-HBc is detected, the result appears to be a false positive. Data from several studies have demonstrated that a primary anti-HBs response develops in most of these persons after a three-dose series of hepatitis B vaccine.

HBeAg can be detected in the serum of persons with acute or chronic HBV infection. The presence of HBeAg correlates with viral replication and high levels of virus (i.e., high infectivity). Anti-HBe correlates with the loss of replicating virus and with lower levels of virus, although reversion to HBeAg-positivity has been observed in 14% of HBeAg-negative, anti-HBe-positive persons with chronic infection. All HBsAg-positive persons should be considered potentially infectious regardless of their HBeAg or anti-HBe status.

Qualitative or quantitative nucleic acid tests can detect HBV DNA during acute and chronic infection. These tests are not FDA-approved and are most commonly used for patients being managed with antiviral therapy.

Infection or immunization with one subtype of HBV confers immunity to all subtypes. However, reinfection or reactivation of latent HBV infection has been reported among certain groups of immunosuppressed persons, including renal transplant recipients and persons infected with HIV. Case reports have described persons who were positive for antibody to hepatitis B core antigen (anti-HBc), with or without antibody to HBsAg (anti-HBs) and subsequently developed detectable levels of HBsAg. The frequency with which this phenomenon occurs is unknown.

Epidemiology of Hepatitis B Virus Infection

Transmission

HBV is transmitted by percutaneous (i.e., puncture through the skin) or permucosal (i.e., direct contact with mucous membranes) exposure to infectious blood or to body fluids that contain blood. All HBsAg-positive persons are potentially infectious, but those who are also positive for HBeAg are more infectious because their blood contains high titers of HBV (up to 10^9 virions/mL). When virus titers are this high, body fluids containing serum or blood can also contain high levels of HBV and are potentially infectious. Although HBsAg has been detected in a variety of body fluids, only serum, semen, and saliva have been demonstrated to be infectious.

HBV is relatively stable in the environment and remains viable for at least 7 days on environmental surfaces at room temperature. HBV at titers of $10^{2–3}$ virions/mL can be present on environmental surfaces in the absence of any visible blood and still cause transmission. Thus, blood-contaminated surfaces or fomites represent a reservoir for HBV transmission.

Prospective cohort and case-control studies have identified risk factors associated with acquisition of HBV infection in the United States. These risk factors, which occurred during the incubation period, included receipt of blood transfusion or organ or tissue transplant from an infectious donor; illegal injection-drug use, including sharing of injection-preparation equipment; male sexual activity with other men; unprotected sex with an infected partner; unprotected sex with more than one partner; birth to an infected mother; and healthcare employment involving

frequent exposure to blood or needles. Outbreaks of HBV infections due to contaminated equipment used for therapeutic injections and other healthcare-related procedures, tattooing, and acupuncture have been reported, although such exposures are rarely reported among patients with acute hepatitis B. No infections have been demonstrated in susceptible persons who were orally exposed to HBsAg-positive saliva, but transmission has occurred through a human bite and has been demonstrated in animals by subcutaneous inoculation of saliva.

Donor selection procedures and routine testing of donors for HBsAg and anti-HBc have made transmission of HBV via transfusion of whole blood and blood components a rare occurrence, and transmission via plasma-derived products has been eliminated through viral inactivation procedures. Among persons with bleeding disorders cared for at U.S. hemophilia treatment centers during 1998-2002, no infections with viral hepatitis, including HBV, were attributable to blood products received during that time. HBV transmission by organs or tissue is also rare.

Patient-to-patient transmission of HBV has been identified in a variety of healthcare settings, including chronic hemodialysis centers, inpatient services, outpatient clinics, and long-term care facilities. In most cases, transmission resulted from noncompliance with aseptic techniques for administering injections and recommended infection control practices designed to prevent cross-contamination of medical equipment and devices.

Although HBV infection was recognized as a frequent occupational hazard among persons who worked in laboratories or were exposed to blood while caring for patients, hepatitis B vaccination of healthcare workers and implementation of standard precautions has made HBV infection a rare event in these populations. HBV transmission from infected healthcare

personnel to patients is also relatively uncommon. Most of the reported cases occurred before 1991 and involved transmission of HBV from infected surgeons or dentists during the performance of invasive procedures. A few cases involved other types of healthcare providers with skin conditions (e.g., exudative dermatitis, bleeding lesions or cuts).

The risk of perinatal HBV transmission for infants born to HBsAg-positive women who are HBeAg-positive ranges from 70% to 90% at 6 months of age; about 90% of these children remain chronically infected. The risk of perinatal infection among infants born to HBsAg-positive, HBeAg-negative mothers ranges from 10% to 40%, with 40%-70% of these infected infants remaining chronically infected. Limited data indicate that mode of delivery (i.e., caesarean versus vaginal) does not affect the risk of perinatal transmission of HBV. Children born to HBsAg-positive mothers who do not become infected during the perinatal period remain at high risk of infection during early childhood; in one study, 40% of infants who were not infected perinatally became infected by age 5 years. No data indicate that breastfeeding poses an increased risk for infection.

Among adults, sexual activity is a frequent route of HBV transmission. Infection among MSM has been associated with receptive anal intercourse, increased numbers of sex partners, and increased years of sexual activity. Factors associated with increased risk of HBV infection among heterosexual men and women include number of sex partners, number of years of sexual activity, and history of other STDs. In follow-up studies of the susceptible sex partners of persons with acute hepatitis B, HBV infection developed in 18%-30%. Among susceptible spouses of persons with chronic HBV infection, the seroprevalence of HBV infection has ranged from 25% to 59%.

HBV infections have not been documented in nonsexual household contacts of persons with acute hepatitis B. However, person-to-person spread of HBV can occur in settings involving nonsexual interpersonal contact over a long period, such as among household contacts of chronically infected persons. In follow-up studies of the susceptible household contacts of children with chronic HBV infection, new HBV infections developed in 14%-60% of contacts. Data from cross-sectional studies also demonstrate that household contacts of HBV-infected persons are more likely to have serologic markers of HBV infection (25%-30%) than the household contacts of persons not infected with HBV (2%-8%). In these studies, infected contacts included all types of relationship categories. When the chronically infected person was a child, serologic evidence of HBV infection was more common in other children in the household than in adults. When the chronically infected person was an adult, seropositivity for HBV was more common in other adults in the household (e.g., spouses, siblings, parents) than in children.

Person-to-person transmission is households of chronically infected persons accounts for high rates of infection among Alaskan Natives, Pacific Islanders, and children born to women who immigrated to the United States from countries where HBV infection is highly endemic (**Figure 1**) before implementation of routine infant hepatitis B vaccination. In rare instances, person-to-person transmission has also been reported in child daycare centers and schools. Before routine infant vaccination was implemented, an estimated 16,000 children <10 years of age were infected with HBV each year, beyond the postnatal period. Although these early childhood infections represented only 5% of all HBV infections, they are estimated to result in 18% of chronic HBV infections among persons who acquired their infections in the United States

(**Figure 2).** The majority of these childhood infections occurred among children born to HBsAg-negative mothers and would not have been prevented by HBsAg testing of pregnant women and postexposure immunoprophylaxis of infants born to seropositive women (See: Prevention of perinatal transmission and management of pregnant women).

Although the precise mechanisms of non-sexual household transmission are unknown, frequent interpersonal contact of nonintact skin or mucous membranes with blood containing secretions or perhaps saliva are the most likely modes of transmission. One study found that HBV infection was more likely to develop in family members of chronically infected persons who shared toothbrushes or partially eaten food. Because of the extremely high concentration of virus in blood, the number of virions in even very small amounts of blood or body fluids can be quite high. In addition, HBsAg contamination of surfaces is widespread in homes of chronically infected persons, and HBV remains infectious for long periods under ambient conditions.

Recent studies have demonstrated that sexual activity accounts for 61% of HBV transmission in the United States and injection-drug use for 18%. Other known exposures (occupational, household, healthcare-related) together account for 5%. Among the 16% of persons with acute hepatitis B who deny a specific risk factor for infection, 40% reported previous high-risk drug or sexual behaviors that might have placed them at risk for HBV infection.

Incidence

Since the 1991 adoption of a comprehensive strategy to eliminate HBV transmission in the United States, the incidence of acute hepatitis B has declined steadily, by 67% overall and by

89% in children and adolescents (**Figure 3**). Declines have been greatest among children born after 1991; it is estimated that at least 6,000 perinatal infections and 16,000 childhood infections have been prevented annually in the United States since routine childhood immunization was implemented. In addition to declines by age, racial disparities in hepatitis B incidence have narrowed (**Figure 4**). The reduction of the disparity between Asian/Pacific Islanders and other children is consistent with recent observations noting a decline in seroprevalence of HBV infection and successful implementation of routine hepatitis B vaccination among Asians who have recently immigrated to the United States. The incidence of acute hepatitis B declined among all adults during 1990-1998, but increased 5% among males aged 20-39 years and 20% and 31%, respectively, among males and females aged >40 years.

Prevalence

Data from two National Health and Nutrition Examination Surveys (NHANES) performed during 1976-1980 (NHANES II) and 1988-1994 (NHANES III) show no significant change in the overall prevalence of HBV infection in the general U.S. population. The overall age-adjusted prevalence was 5.5% in NHANES II and 4.9% in NHANES III. Prevalence increased steadily with age and varied by race/ethnicity. Because Asian/Pacific Islanders contribute disproportionately to the burden of chronic HBV infection in the United States but are not sampled for participation in NHANES, the surveys underestimate the prevalence of chronic infection; after correction, the estimated prevalence of chronic HBV infection is 0.5%. The highest overall prevalence of HBV infection was found in non-Hispanic blacks (NHANES II: 15.8%; NHANES III: 11.9%), and the strongest associations with HBV infection were black race, increasing number of lifetime sex partners, and foreign birth. No data were available

regarding sexual preference or injection-drug use. In addition to variations in prevalence by age and race/ethnicity, there is substantial variation based on country of birth and risk behavior.

PROPHYLAXIS AGAINST HEPATITIS B VIRUS INFECTION

HBV infection and disease can be prevented through immunization with vaccines that contain HBsAg and induce the formation of protective antibody (anti-HBs). Temporary immunity may also be obtained using hepatitis B immune globulin (HBIG) for postexposure prophylaxis.

Hepatitis B Vaccine

Composition and formulations

HBsAg is the antigen used for hepatitis B immunization. Vaccine antigen can be purified from the plasma of persons with chronic HBV infection or produced by recombinant DNA technology. Vaccines currently available in the United States use recombinant DNA technology to express HBsAg in yeast, which is then purified from the cells by biochemical and biophysical separation techniques. Hepatitis B vaccines licensed in the United States are formulated to contain 10-40 µg of HBsAg protein/mL. Since March 2000, hepatitis B vaccines produced for distribution in the United States do not contain thimerosal as a preservative, although one contains a trace of mercury (<0.5 mcg/dose) from the manufacturing process. Hepatitis B vaccine should be stored at 35-46^{o} F (2-8^{o} C) and should not be frozen.

Hepatitis vaccine is available as a single-antigen formulation and also in fixed combination with other vaccines. Two single-antigen vaccines are available in the United States: RECOMBIVAX

HB® (manufactured by Merck & Co., Inc.) and ENGERIX-B® (manufactured by GlaxoSmithKline). Of the three licensed combination vaccines, one is used for vaccination of adults (TWINRIX®) and two for vaccination of infants and young children (COMVAX®, PEDIARIX™). TWINRIX (manufactured by GlaxoSmithKline) contains recombinant HBsAg and inactivated hepatitis A virus. COMVAX (manufactured by Merck & Co., Inc.) contains recombinant HBsAg and Hib polyribosylribitol phosphate (PRP) conjugated to *Neisseria meningitidis* outer membrane protein complex (OMPC). PEDIARIX (manufactured by GlaxoSmithKline) contains recombinant HBsAg, diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP), and inactivated poliovirus (IPV).

Dose and administration

Recommended vaccine doses vary by product, age of recipient, and needs of special populations (**Table 2**). Providers must always follow the manufacturer's dosage recommendations. Although the antigen contents of the vaccines differ, vaccines made by different manufacturers are interchangeable, except for the two-dose schedule used for adolescents aged 11-15 years; only RECOMBIVAX HB is approved for this schedule. Combination vaccines are not approved for use as a birth dose because of potential suppression of the immune response to subsequent doses of the Hib component in COMVAX and possible decreased immunogenicity of the diphtheria component of PEDIARIX when administered at birth.

Hepatitis B vaccine is administered by intramuscular injection. The anterolateral thigh muscle is the recommended site of administration for neonates (aged <1 month) and for infants (aged <12 months). For toddlers (aged 1-2 years) and older children, either the anterolateral thigh or the deltoid muscle may also be used if the muscle mass is adequate. The deltoid muscle is the

preferred site of administration for adolescents and adults. The recommended needle length for administration of hepatitis B vaccine is 7/8-1" for infants and 7/8-1¼" for toddlers and older children. For adolescents and adults, the needle length should be 1-2" depending on the recipient's weight (1" for females weighing <70 kg; 1.5" for males weighing <120 kg; 2" for males weighing >120 kg and females >100 kg. A 22- to 25-gauge needle is recommended.

Injection into the buttock is associated with decreased immunogenicity and is not recommended. Intradermal administration can result in a lower seroconversion rate and final titer of anti-HBs compared to intramuscular administration, and no data are available to assess long-term protection from this route of administration. Hepatitis B vaccine administered by any route or site other than intramuscularly in the anterolateral thigh or deltoid muscle should not be counted as valid and should be repeated, unless serologic testing indicates that an adequate response has been achieved (See: Postvaccination testing for serologic response).

Hepatitis B vaccine and other vaccines administered during the same visit should be given in different injection sites. When more than one injection must be given in the same limb, the anterolateral thigh is usually the preferred site, with injections separated by 1-2" to avoid overlap in local reactions. In persons with bleeding disorders, the risk of bleeding after intramuscular injection can be minimized by administration of vaccine immediately after infusion of coagulation factor, use of a 23-gauge (or smaller) needle, and application of direct pressure to the injection site for at least 2 minutes.

Immunogenicity

A complete vaccine series induces a protective level of antibody (≥10 mIU/mL) in >95% of

healthy infants, children, and adolescents and in >90% of healthy adults <40 years of age. After age 40, the proportion of persons developing a protective antibody response drops below 90%, and by age 60, only 75% of vaccinees develop protective levels of antibody. Host factors in addition to age that contribute to decreased vaccine response include smoking, obesity, and immune suppression (See*:* Groups requiring different vaccination doses or schedules*)*.

Administration of single-antigen or combination vaccine simultaneously with other childhood or adult vaccines produces no clinically significant interference in antibody responses. No differences in immunogenicity have been observed when one or two doses of hepatitis B vaccine produced by one manufacturer are followed by doses from a different manufacturer.

Correlates of protection

Anti-HBs is the only easily measurable correlate of vaccine-induced protection. Persons who develop anti-HBs ≥10 mIU/mL after preexposure vaccination achieve virtually complete protection against both acute and chronic infection. Although immunogenicity is lower among immunocompromised persons, those who achieve a protective antibody response before exposure to HBV have a high level of protection from infection.

Antibody decline

After primary immunization with hepatitis B vaccine, anti-HBs levels decline rapidly within the first year and more slowly thereafter. Among children and young adults who respond with a protective antibody level to a primary vaccine series, 17%-50% have low or undetectable levels of anti-HBs (anti-HBs loss) 10-15 years after vaccination. Similarly, 15%-76% of children who

respond to a primary vaccine series started at birth have low or undetectable antibody levels 10-15 years after vaccination. The persistence of detectable anti-HBs after vaccination is related to the level of post-vaccination antibody titers. Peak antibody levels after a primary series are highest in young adults and adolescents and lower for children immunized as infants compared to children immunized at >12 months of age.

Immune memory

Despite declines in anti-HBs to less than protective levels, immunized persons are still protected against HBV infection. The mechanism for continued vaccine-induced protection is thought to be the preservation of immune memory through selective expansion and differentiation of clones of antigen-specific B and T lymphocytes. When anti-HBs levels fall below 10 mIU/mL, an additional dose of hepatitis B vaccine has been shown to elicit a rapid rise in antibody (anamnestic response), providing indirect evidence of immune memory. Persistence of vaccine-induced immune memory among immunocompetent children and adults who responded to a primary vaccine series as long as 13 years earlier has been demonstrated by a rapid fourfold or greater rise in anti-HBs 2-4 weeks after administration of an additional vaccine dose; 35% to 100% of study participants had undetectable anti-HBs before antigen challenge. Although direct measurement of immune memory is not yet possible, these data indicate that a high proportion of vaccinees retain immune memory and would mount an anti-HBs response upon exposure to HBV. The primary vaccine series apparently recruits sufficient immune memory to produce an ananmestic response to an antigen challenge for at least 10-13 years, even when anti-HBs fall to low or undetectable levels.

Duration of vaccine-induced protection

Studies of cohorts of vaccinated, immunocompetent adults, children, and infants indicate that, despite anti-HBs loss many years after immunization, nearly all vaccinated persons who respond to a primary series remain protected from HBV infection. No clinical cases of hepatitis B have been observed in 15- to 20-year follow-up studies among immunocompetent vaccinated populations, and only rare chronic infections have been documented. Most breakthrough infections have been observed among vaccinated infants born to HBsAg-positive women; no chronic infections have been observed among adults who responded to vaccination (**Table 3**). In some studies, breakthrough infections detected by the presence of anti-HBc have been documented in a small percentage of persons, but these transient asymptomatic infections are unlikely to be a source of transmission and are not associated with development of chronic liver disease or HCC.

Hepatitis B Immune Globulin (HBIG)

HBIG provides passively acquired anti-HBs and temporary protection (i.e., 3-6 months) when administered in standard doses. HBIG is usually used as an adjunct to hepatitis B vaccine for postexposure immunoprophylaxis to prevent HBV infection. HBIG administered alone is the primary means of protection after an HBV exposure for nonresponders to hepatitis B vaccination. In addition, long-term administration of HBIG is used to prevent recurrence of HBV infection in liver transplant recipients.

Composition

HBIG is prepared from the plasma of donors with high concentrations of anti-HBs. The plasma

from which HBIG is prepared is screened for HBsAg, antibodies to HIV and HCV and for HCV RNA. In addition, the process used to manufacture HBIG inactivates viruses (e.g., HBV, HCV, HIV) from the final product. No evidence exists that HBV, HCV, or HIV have ever been transmitted by HBIG commercially available in the United States. HBIG should be stored at 35-46° F (2-8° C) and should not be frozen.

Dose and administration

The standard dose of HBIG is 0.5 mL for postexposure prophylaxis of infants born to HBsAg-positive women and 0.06 mL/kg for all other applications. HBIG can be administered simultaneously with hepatitis B vaccine but in a different injection site. For infants, HBIG is administered intramuscularly in the anterolateral thigh using a 22- to 25-gauge needle that is 7/8-1" in length. For older children, adolescents, and adults, an appropriate muscle mass (i.e., deltoid, gluteal) should be chosen in which to deliver the larger volumes of HBIG required for these age groups, using a needle length appropriate for the person's age and size.

IMMUNIZATION SCHEDULES AND RESULTS OF IMMUNIZATION

Preexposure Vaccination

Infants and children

Primary vaccination consists of at least three intramuscular doses of hepatitis B vaccine. Vaccine schedules for infants and children (**Table 4**) were developed based on immunogenicity data and the need to integrate hepatitis B vaccine into a harmonized childhood immunization

schedule. Although not all possible schedules for each product have been evaluated in clinical trials, currently licensed formulations for both single-antigen vaccines have been shown to produce high (>95%) levels of seroprotection among infants, children, and adolescents when administered in a variety of schedules. Administration of the final dose to infants is not recommended before age 24 weeks, to achieve final antibody levels among infants vaccinated at birth that are comparable to those attained when immunization is initiated at 1-2 months of age.

The immunogenicity of the combined hepatitis B-Hib conjugate vaccine (COMVAX) and the combined hepatitis B-DTaP-IPV vaccine (PEDIARIX) is equivalent to that of their individual antigens administered separately. However, these vaccines cannot be administered to infants before the age of 6 weeks; only single-antigen hepatitis B vaccine may be used for the birth dose. A vaccine series started with a birth dose of single-antigen vaccine can, however, be completed with three doses of combination vaccine (**Table 4).** Administration of a total of four doses of hepatitis B vaccine has been shown to be safe in clinical trials. Anti-HBs responses after a three-dose series of hepatitis B-containing combination vaccines among infants who were previously vaccinated at birth are comparable to those observed after a three-dose series of combined hepatitis B-Hib vaccine without a birth dose.

Adolescents

Recommended vaccination schedules for adolescents (**Table 4**) balance available immunogenicity data with the need to achieve compliance with vaccination in this age group. Both licensed single-antigen vaccines administered intramuscularly at 0, 1, and 6 months produce a >95% seroprotection rate in adolescents. Equivalent seroprotection rates are achieved among adolescents vaccinated at 0, 1-2, and 4 months and 0, 12, and 24 months. The adult (10

μg) dose of RECOMBIVAX-HB administered in a two-dose schedule to 11- to 15-year-olds at 0 and 4-6 months produces antibody levels equivalent to those obtained with the 5-μg dose administered on a three-dose schedule. However, no data on long-term antibody persistence or protection are available for this schedule. No combination vaccines are approved for use in adolescents <18 years of age.

Adults

The three-dose vaccine series administered intramuscularly at 0, 1, and 6 months produces a protective antibody response in approximately 30%-55% of healthy adults <40 years of age after the first dose, 75% after the second dose, and >90% after the third dose. Several alternative vaccine schedules (**Table 4**) have been evaluated and found to elicit dose-specific and final rates of seroprotection similar to those obtained on a 0, 1, 6-month schedule.

The combined hepatitis B-hepatitis A vaccine (TWINRIX) is indicated for vaccination of adults ≥18 years of age with risk factors for both hepatitis B and hepatitis A. The dosage of the hepatitis A component in the combined vaccine is lower than that in the single-antigen hepatitis A vaccine, allowing it to be administered in a three-dose schedule instead of the two-dose schedule used for the single-antigen vaccine.

Minimum dosing intervals and off-schedule doses

No apparent effect on immunogenicity has been documented when minimum spacing of doses is not achieved precisely. Increasing the interval between the first and second doses has little effect on immunogenicity or final antibody concentration, although few data exist on intervals of

>2 months. The third dose confers the maximum level of seroprotection but acts primarily as a booster and appears to provide optimal long-term protection; longer intervals between the last two doses result in higher final antibody levels.

Response to revaccination

Of persons who do not respond to a primary vaccine series, 25%-50% respond to an additional vaccine dose and 50%-75% respond to a three-dose revaccination series given on a 0, 1, 6-month schedule. Persons who fail to develop a protective level of anti-HBs 1-2 months after revaccination either are primary nonresponders or are infected with HBV. No data suggest that persons who fail to develop detectable antibody after six doses of vaccine would benefit from additional doses.

Groups requiring different vaccination doses or schedules

Preterm infants: Preterm infants weighing <2,000 grams at birth have a decreased response to hepatitis B vaccine given before 1 month of chronological age. By chronological age 1 month, most medically stable preterm infants, regardless of initial birth weight or gestational age, have a response to vaccination that is comparable to that of full-term infants.

Hemodialysis patients: Compared to immunocompetent adults, a lower proportion of hemodialysis patients develop protective levels of antibody after vaccination with standard vaccine dosages. Among adult hemodialysis patients, 67%-86% (median: 64%) of those who receive either a three-dose or a four-dose series (**Table 2**) develop protective levels of antibody. Some studies have demonstrated higher seroprotection rates in patients with chronic renal

failure, particularly those with mild or moderate renal failure, who are vaccinated before becoming dialysis dependent. After vaccination with a four-dose series (**Table 2**), the seroprotection rate among adult predialysis patients with serum creatinine levels of ≤4.0 mg/dL was 86%, compared to 37% among patients with serum creatinine levels above 4.0 mg/dL, of whom 88% were dialysis patients.

Although data on the response of pediatric hemodialysis patients to vaccination with standard pediatric doses are lacking, 75%-97% of those who received the higher dosages on either the three- or four-dose schedule develop protective levels of antibody. In the one study that evaluated vaccine response among children with chronic renal failure, high seroprotection rates were achieved with four 20-µg doses in both predialysis and dialysis-dependent patients, although predialysis patients had higher peak antibody concentrations.

HIV-infected persons: Humoral response to hepatitis B vaccination is reduced in children and adults with HIV infection. Some studies have found increased response rates in persons with higher $CD4^+$ cell counts. Modified dosing regimens in children and adults, including a doubling of the standard antigen dose, and administration of additional doses may increase response rates.

Other immunocompromised persons: Other immunocompromised persons (e.g., hematopoietic stem cell transplant recipients) may also have a suboptimal response to standard doses of hepatitis B vaccine and may require larger doses to induce protective antibody levels. However, few data on the response to higher vaccine doses in these patients are available.

Postexposure Prophylaxis

After exposure to HBV, early prophylactic immunization can prevent acquisition of infection in non-immune persons. The mainstay of postexposure prophylaxis is active immunization with hepatitis B vaccine. In some situations, passive-active immunization with hepatitis B vaccine and HBIG may provide increased protection, and passive immunization with HBIG alone is recommended in some settings for persons who do not respond to hepatitis B vaccination.

Perinatal HBV exposure

Passive-active prophylaxis: Passive-active prophylaxis with hepatitis B vaccine and HBIG administered within 12-24 hours after birth, followed by completion of a three-dose vaccine series, has been shown to be 85%-95% effective in preventing acute and chronic HBV infection in infants born to women who are HBsAg- and HBeAg-positive. Although clinical trials have evaluated the efficacy of passive-active immunoprophylaxis administered only within 24 hours of birth, studies of passive immunoprophylaxis have shown that HBIG provides protection when administered as late as 72 hours after exposure. Most clinical trials have evaluated the efficacy of passive-active postexposure prophylaxis when the second vaccine dose is administered at 1 month of age. A clinical trial of passive-active prophylaxis that compared vaccination at birth, 1 month, and 6 months to vaccination at birth, 2 months, and 6 months showed comparable efficacy in prevention of acute and chronic infection among infants born to HBsAg/HBeAg-positive mothers.

Infants born to HBsAg-positive, HBeAg-negative mothers who receive passive-active postexposure prophylaxis should have the same high degree of protection as infants born to women who are HBsAg/HBeAg-positive. However, the efficacy of this regimen has not been

examined in controlled clinical trials because the low infection rate would require an unattainable sample size. Although rates of perinatal HBV transmission are higher from HBeAg-positive mothers compared to HBeAg-negative mothers, testing of HBsAg-positive pregnant women for HBeAg is not warranted for the management of the infant because postexposure prophylaxis is recommended for all infants born to HBsAg-positive women.

Data on the effectiveness of postexposure prophylaxis combined with universal hepatitis B immunization in preventing HBV infection indicate that >98% of infants are protected from infection. The major determinant of effectiveness is on-time administration of the initial doses of vaccine and HBIG. No data are available on the efficacy of HBsAg-containing combination vaccines when used to complete the vaccine series for postexposure prophylaxis to prevent perinatal HBV infection. However, the efficacy of combination vaccines is expected to be similar to that of single-antigen vaccines because the HBsAg component induces a comparable anti-HBs response. Thus, although not indicated in the manufacturer's package labeling, HBsAg-containing combination vaccines may be used for infants (≥6 weeks of age) born to HBsAg-positive mothers to complete the vaccine series after receiving a birth dose of single-antigen hepatitis B vaccine.

Active prophylaxis: Active postexposure prophylaxis with hepatitis B vaccine alone (i.e., without HBIG) is widely used in areas where implementation of maternal HBsAg testing is difficult (e.g., Alaska, Pacific Islands, developing countries). In randomized, placebo-controlled clinical trials, administration of hepatitis B vaccine in a three- or four-dose schedule, without HBIG, beginning within 12 hours after birth has been shown to prevent 70%-95% of perinatal HBV infections among infants born to HBsAg/HBeAg-positive women. Population-based

studies in areas with a high endemicity of HBV infection have shown that active postexposure vaccination is highly effective in preventing infection when the first dose is given soon after birth, the second at 1-2 months of age, and the third at 6-8 months of age.

Other exposures

Controlled clinical trials have established the efficacy of hepatitis B vaccine with or without HBIG for prevention of acute and chronic HBV infection in most other exposure situations. In addition, two large multicenter trials demonstrated that postexposure administration of HBIG alone protected against an estimated 75% of HBV infections following needlestick exposures to HBsAg- and HBeAg-positive blood. Limited data suggest that passive-active prophylaxis may be more effective than active prophylaxis for sex partners of persons with acute hepatitis B. The effectiveness of postexposure immunoprophylaxis administered >7 days after percutaneous exposure is unknown. One study found that HBIG alone was effective when administered within 14 days after sexual exposure. For situations for which clinical trial data are lacking, postexposure recommendations either are based on available effectiveness data or are extrapolated from the results of clinical trials conducted in situations characterized by high levels of HBV exposure (e.g., perinatal exposure).

Substantial evidence suggests that adults who respond to hepatitis B vaccination are protected from chronic HBV infection for as long as 20 years, even if vaccinees lack detectable anti-HBs at the time of an exposure (See: Duration of vaccine-induced protection). Thus, persons known to have responded to hepatitis B vaccination do not require additional passive or active immunization following an HBV exposure.

VACCINE SAFETY

Hepatitis B vaccines have been shown to be safe when administered to infants, children, adolescents, and adults. In the United States, an estimated 30-50 million adults and adolescents and >40 million infants and children have been vaccinated.

Vaccine Reactogenicity

The most frequently reported side effects among adults and children receiving hepatitis B vaccine are pain at the injection site (3%-29%) and temperature >37.7 C (1%-6%). In placebo-controlled studies, however, these side effects were reported no more frequently among persons receiving hepatitis B vaccine than among persons receiving placebo. Administration of hepatitis B vaccine soon after birth has not been associated with an increased rate of elevated temperatures or sepsis evaluations.

Adverse Events

A review by the Institute of Medicine found evidence for a causal association between receipt of hepatitis B vaccine and anaphylaxis. Based on data from the Vaccine Safety Datalink (VSD) project, the estimated incidence of anaphylaxis among children and adolescents who received hepatitis B vaccine is 1 per 1.1 million vaccine doses distributed (95% CI: 0.1-3.9). Although a population-based study found no statistical association between alopecia (hair loss) and hepatitis B vaccine, reported episodes of alopecia following rechallenge with hepatitis B vaccine suggest that vaccination may, in rare cases, trigger episodes of alopecia. No evidence of a causal

association has been demonstrated for other adverse events reported after hepatitis B vaccination.

Early postlicensure surveillance of adverse events showed a possible association between Guillain-Barre syndrome and receipt of the first dose of plasma-derived hepatitis B vaccine among U.S. adults. However, in a subsequent analysis of Guillain-Barre syndrome cases reported to CDC, the FDA, and vaccine manufacturers among an estimated 2.5 million adults who received one or more doses of recombinant hepatitis B vaccine from 1986 to 1990, the rate of Guillain-Barre syndrome occurring after hepatitis B vaccination did not exceed the background rate among unvaccinated persons.

Multiple sclerosis (MS) has been reported after hepatitis B vaccination among adults but has not been reported among children. Although one retrospective case-control study found an association between hepatitis B vaccine and MS among adults, multiple other studies have shown no association, and a case-crossover study showed no association between vaccination (including hepatitis B vaccination) and short-term relapse in patients with MS. Reviews by expert panels have concluded that available data favor rejection of a causal association between hepatitis B vaccination and MS.

Chronic illnesses that have been reported in rare instances following hepatitis B vaccination include asthma, chronic fatigue syndrome, optic neuritis, rheumatoid arthritis, type 1 diabetes, and autoimmune disease. No evidence of a causal association between these conditions and hepatitis B vaccine has been demonstrated, but data are limited.

In rare instances, infant deaths have been reported after hepatitis B vaccination, but multiple studies have found no evidence of a causal association between hepatitis B vaccination, including administration of the birth dose, and sudden infant death syndrome (SIDS) or other causes of death in the first year of life. Infant death rates, including rates of SIDS, declined substantially in the United States during the 1990s, coincident with increases in infant hepatitis B vaccination coverage from <1% to >90%.

The safety of hepatitis B vaccine will continue to be assessed through ongoing monitoring of data from VSD, the Vaccine Adverse Events Reporting System (VAERS), and other surveillance systems. All adverse events suspected to be associated with hepatitis B vaccination should be reported to VAERS. Report forms and assistance are available by calling 1-800-822-7967 or at http://www. fda.gov/cber/vaers.htm.

Contraindications and Precautions

Hepatitis B vaccination is contraindicated for persons with a history of allergic reactions to yeast or any vaccine component. Despite a theoretical risk of allergic reaction to vaccination in persons with allergy to *Saccharomyces cerevisiae* (baker's yeast), evidence documenting adverse reactions after vaccination of persons with a history of yeast allergy is lacking.

Persons with a history of serious adverse events, including anaphylaxis, after receipt of hepatitis B vaccine should not receive additional doses. As with other vaccines, vaccination of persons with moderate or severe acute illness, with or without fever, should be deferred until the illness improves. Vaccination is not contraindicated in persons with a history of MS, Guillain-Barre

syndrome, or autoimmune disease (e.g., systemic lupus erythematosis, rheumatoid arthritis).

Pregnancy is not a contraindication to vaccination. Limited data indicate no apparent risk of adverse events to developing fetuses when hepatitis B vaccine is administered to pregnant women. The vaccine contains noninfectious HBsAg and should cause no risk to the fetus.

STRATEGY TO ELIMINATE HBV TRANSMISSION: IMPLEMENTATION AND CHALLENGES

In 1982, the Advisory Committee on Immunization Practices (ACIP) first recommended hepatitis B vaccination for infants born to HBV-infected mothers; in 1988, the recommendation was expanded to include all infants in racial/ethnic groups with high rates of chronic HBV infection. By the early 1990s, accumulating data showed that many children remained at risk for HBV infection because of incomplete maternal screening and the occurrence of a substantial proportion of infections in children of HBsAg-negative mothers. Furthermore, hepatitis B surveillance data indicated that the incidence of acute disease had continued to increase because high-risk adults and adolescents were not being vaccinated. With these data and a growing body of evidence that hepatitis B vaccination was safe, ACIP expanded its hepatitis B immunization recommendations in 1991 to include all infants – in the short term to stop HBV transmission among children and in the long term to prevent HBV infections in adolescents and adults. To achieve a more rapid impact on the incidence of disease, the elimination strategy was expanded in 1995 to include routine vaccination of all adolescents aged 11-12 years and, in 1999, to include children aged <18 years who had not been vaccinated previously.

To date, most of these components of the national strategy to eliminate HBV transmission have been widely implemented. Hepatitis B vaccine has been successfully integrated into the childhood vaccine schedule, and infant vaccine coverage levels are now equivalent to those of other vaccines in the childhood schedule. As of 2003, >92% of 19- to 35-month-old children had been fully immunized with three doses of hepatitis B vaccine. Part of this success can be attributed to the established infrastructure for vaccine delivery to children, which ensures high coverage levels. Because hepatitis B vaccine provides long-term protection against chronic HBV infection, these children will be protected as they move through adolescence and adulthood.

Vaccine coverage among adolescents has increased substantially. In response to the 1995 recommendation for routine hepatitis B immunization of adolescents, a growing number of states are requiring vaccination for middle-school entry, and a number of programs provide hepatitis B vaccine to high-risk youth. Preliminary vaccine coverage data from 2002 indicate that >70% of 13- to 15-year-olds have been vaccinated against hepatitis B.

High HBsAg screening rates have also been achieved among pregnant women. Currently, every state and large metropolitan area receives federal funding to support perinatal hepatitis B prevention programs, and >95% of pregnant women are tested for HBsAg. However, only about 50% of expected births to HBsAg-positive women (**Table 6**) are identified for case management, which has been effective in ensuring high levels of initiation and completion of postexposure immunoprophylaxis. For women without prenatal care, the need for proper management, including HBsAg testing of the mother at the time of admission for delivery and administration of the first dose of hepatitis B vaccine to the infant within 12 hours of birth, is underscored by

the higher prevalence of HBsAg seropositivity in this group compared to women who are screened prenatally. However, studies have found that infants born to mothers with unknown HBsAg status at the time of delivery often do not receive a birth dose. In addition, errors in maternal HBsAg testing and omissions in test reporting have resulted in failure to administer postexposure immunoprophylaxis to infants born to HBsAg-positive mothers.

The greatest remaining challenge for hepatitis B prevention is the vaccination of high-risk persons. Most HBV transmission and the morbidity associated with acute hepatitis B occurs among young adults, most of whom acquire their infections through sexual activity; persons with high-risk sexual behaviors account for more than half of newly acquired cases of hepatitis B. Despite longstanding recommendations for vaccination of persons who report a history of multiple sex partners, STD treatment, or male sexual activity with another male, vaccine is rarely offered in settings that provide health care to adults, including settings that provide services targeted specifically to high-risk adults (e.g., STD treatment clinics, HIV counseling and testing programs, drug treatment centers). As a result, many opportunities to vaccinate high-risk adults are missed. For example, approximately 60% of adults with acute hepatitis B report previously receiving care in a setting were vaccination is recommended, such as an STD clinic, drug treatment center, or correctional facility. Thus, efforts to vaccinate adults at increased risk for hepatitis B infection need to be greatly expanded to accelerate elimination of HBV transmission.

FUTURE CONSIDERATIONS

Implementation of the recommendations included in this document should ultimately lead to the elimination of HBV transmission in the United States. New information will have implications for this effort, and adjustments and changes are expected to occur. Some of the issues that can be expected to be addressed in clinical and operational studies include the following.

Long-Term Protection and Booster Doses

Further studies are needed to assess long-term protection after vaccination and the possible need for booster doses of vaccine. The longest follow-up studies of vaccine protection have been conducted in populations with an initially high endemicity of HBV infection (i.e., >8% prevalence of chronic infection). In most of these populations, widespread hepatitis B vaccination programs have resulted in virtual elimination of new HBV infections and a dramatic decrease in HBV infection pressure, which will complicate future efforts to assess hepatitis B vaccine efficacy. Assessment of efficacy provided by hepatitis B immunization after 15-20 years will require studies among populations that continue to have exposures to HBsAg-positive persons (e.g., communities of immigrants from highly endemic countries; populations of injection-drug users, MSM, or healthcare workers) and studies among populations with a low prevalence of infection.

Vaccine Coverage among Adults

The prevalence of immunity to HBV infection among adults will increase over the next decade because of increased adolescent and childhood vaccination coverage. Further studies are needed to determine how to assess vaccination histories in settings where provision of written evidence of vaccination is not feasible (e.g., correctional facilities, STD clinics), including whether persons should be considered immune if they were likely to have been vaccinated in the context of recommended childhood vaccination programs (e.g., required vaccination for preschool or middle school entry) in the state in which they attended school. Studies are also needed to assess how to perform prevaccination serologic testing in such populations, if indicated.

Immunization Escape Mutants

Although no evidence suggests that S gene immunization escape mutants pose a threat to hepatitis B immunization programs with existing vaccines, further studies and enhanced surveillance to detect the emergence of these variants are high priorities for monitoring the effectiveness of current immunization strategies.

RECOMMENDATIONS FOR ELIMINATION OF HBV TRANSMISSION

Prevention of Perinatal HBV Infection and Management of Pregnant Women

Recommendations

Prenatal HBsAg testing

1. All pregnant women should be routinely tested for HBsAg during an early prenatal visit in *each* pregnancy, even if they have been previously vaccinated.
2. Testing should be repeated in late pregnancy for unvaccinated HBsAg-negative women who are at high risk for HBV infection (e.g., injection-drug users, women with STDs, women with multiple sex partners) or who have had clinical hepatitis since previous testing (See: Vaccination of pregnant women).
3. Women found to be HBsAg positive should be referred to an appropriate case-management program to ensure that their infants receive timely postexposure prophylaxis and follow-up (See: Case-management programs to prevent perinatal HBV infection).
4. For populations in which HBsAg testing of pregnant women is not feasible, *all* infants should receive hepatitis B vaccine within 12 hours of birth and should complete the hepatitis B vaccine series according to a recommended schedule for infants born to HBsAg-positive mothers (**Table 4**).

Management of infants born to women who are HBsAg-positive

1. All infants born to HBsAg-positive women should receive single-antigen hepatitis B vaccine (**Table 4**) and HBIG (0.5 mL) within 12 hours of birth, administered at different injection sites. The three- or four-dose vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers (**Table 4**). The last dose in the vaccine series should not be administered before age 24 weeks (164 days).
2. For preterm infants weighing <2,000 grams, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of hepatitis B vaccine in these infants. Three additional doses of vaccine (for a total of four doses) should be administered beginning when the infant is 1 month of age (**Tables 4 and 5**).
3. Postvaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series.
    - Testing should be performed at 9-15 months of age or 1-2 months after the last dose of vaccine. Testing during these intervals should minimize the likelihood of detecting passively acquired anti-HBs and maximize the likelihood of detecting chronically infected (HBsAg-positive) infants or a response to vaccination.
    - HBsAg-negative infants with anti-HBs levels ≥10 mIU/mL are protected and need no further medical management.
    - HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second three-dose series and retested.
    - Infants found to be HBsAg positive should receive appropriate follow-up (**Appendix A**).
4. Infants of HBsAg-positive mothers may be breast fed.

Management of infants born to women who were not tested for HBsAg

1. Women admitted for delivery without documentation of HBsAg test results should have blood drawn and tested as soon as possible after admission.
2. While test results are pending, all infants born to women without documentation of HBsAg test results should receive the first dose of single-antigen hepatitis B vaccine (without HBIG) within 12 hours of birth (**Table 4**).
   - If the mother is found to be *HBsAg positive*, her infant should receive HBIG as soon as possible but no later than 7 days of age, and the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers (**Table 4**).
   - If the mother is found to be *HBsAg negative*, her infant should continue to receive hepatitis B vaccine according to a recommended schedule for infants born to HBsAg-negative mothers (**Table 4**).
   - If the mother is never tested to determine her HBsAg status, the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers (**Table 4**).
3. Because of the potentially decreased immunogenicity of vaccine in preterm infants weighing <2,000 grams, these infants should receive both single-antigen hepatitis B vaccine and HBIG (0.5 mL), if the mother's HBsAg status cannot be determined within 12 hours of birth. The birth dose of vaccine should not be counted as part of the three doses required to complete the vaccine series; three additional doses of vaccine (for a total of four doses) should be

administered according to a recommended schedule based on the mother's HBsAg test result (**Tables 4 and 5**).

Implementation

Delivery hospital policies and procedures

1. All delivery hospitals should implement policies and procedures to a) ensure identification and initiation of postexposure immunization of infants born to HBsAg-positive mothers and infants born to mothers not screened for HBsAg prenatally, as recommended above (See: Prenatal HBsAg testing), and b) safeguard against errors in maternal HBsAg testing and failures in test reporting. Such policies and procedures should include standing orders for:
   - Review of HBsAg test results for all pregnant women at the time of admission for delivery;
   - For women who do not have a documented HBsAg test result, HBsAg testing as soon as possible after admission for delivery;
   - For all infants born to HBsAg-positive mothers and all infants born to mothers with unknown HBsAg status, administration of appropriate postexposure immunization within 12 hours after delivery (See: Management of infants born to women who are HBsAg positive *and* Management of infants born to women who were not screened for HBsAg prenatally);
   - Administration of hepatitis B vaccination as part of routine care of all medically stable infants with weighing ≥2,000 grams at birth, unless there is a physician's order to defer vaccine based on documentation of a negative maternal HBsAg test result during this pregnancy; and

- Documentation of maternal HBsAg test results and infant hepatitis B vaccination status on the infant's medical record.

2. Delivery hospitals should enroll in the federally funded Vaccines for Children (VFC) program to obtain hepatitis B vaccine at no cost for administration of the birth dose to VFC-eligible newborns.

Case-management programs to prevent perinatal HBV infection

1. Programs, including appropriate policies, procedures, and regulations, should be established to ensure that all pregnant women are tested for HBsAg during each pregnancy and that infants born to HBsAg-positive women and infants born to women with unknown HBsAg status receive recommended case management (see **Box**).
2. The location of these programs and the methods by which they operate will depend on factors such as population density and annual caseload of HBsAg-positive women. Programs may be located at the state or local level in either health departments or private healthcare systems. Program administration will require close collaboration with prenatal care providers, delivery hospital staff, pediatric care providers, private healthcare systems, and health departments.

Components of Case-Management Programs to Prevent Perinatal HBV Infection

Ensure that all pregnant women are tested for HBsAg.

- Practitioners should test all pregnant women for HBsAg during each pregnancy.
- HBsAg testing should be incorporated into standard prenatal testing panels (e.g., blood type, HIV infection, Rh factor, rubella titer, syphilis infection) used by all practitioners caring for pregnant women.
- Delivery hospitals should certify that all pregnant women have been tested for HBsAg before hospital discharge.
- Reporting of HBsAg test status should be included on hospital-based electronic birth certificates or neonatal metabolic screening requests.

Ensure reporting and tracking of HBsAg-positive women.

- All HBsAg-positive pregnant women and all women of childbearing age with HBsAg-positive laboratory results should be reported to state/local perinatal hepatitis B prevention programs.
- All HBsAg-positive pregnant women should be entered into case-management tracking systems.

Ensure receipt of prenatal HBsAg testing records by maternity hospitals prior to delivery.

- HBsAg test results should be included on all forms (hard copy, electronic) used by practitioners to record and transmit information about care during pregnancy.
- Practitioners should document that HBsAg-positive pregnant women have written HBsAg test results transferred from prenatal care providers to the delivery hospital and that patients are informed of their HBsAg test status and advised to notify delivery staff.

Ensure identification and management of infants born to HBsAg-positive mothers and infants born to mothers without HBsAg test results in delivery hospitals.

- Delivery hospitals should implement policies and procedures to ensure identification and initiation of postexposure immunization of infants born to HBsAg-positive mothers and infants born to mothers not screened for HBsAg prenatally; hospitals should safeguard against errors in maternal HBsAg testing and failures in test reporting (See: Delivery hospital policies and procedures).
- Delivery hospitals should document the time of birth and the time of administration of HBIG and hepatitis B vaccine for all infants born to HBsAg-positive mothers.
- Delivery hospitals should document the time of birth, time of administration of hepatitis B vaccine, and maternal HBsAg test results for all infants born to mothers with unknown HBsAg status at the time of delivery.

Ensure completion of hepatitis B vaccine series.

- Practitioners should document the dates of completion of the hepatitis B vaccine series for all infants born to HBsAg-positive mothers.

Ensure completion of postvaccination testing.

- Practitioners should document the results of testing for HBsAg and anti-HBs after completion of the hepatitis B vaccine series for all infants born to HBsAg-positive mothers.

Ensure vaccination of household contacts and sex partners of HBsAg-positive women.

- Household contacts and sex partners of HBsAg-positive pregnant women should be identified.
- If not previously vaccinated or immune to HBV infection, household contacts and sex partners should be offered the hepatitis B vaccine series (See: Postexposure prophylaxis to prevent HBV infection).

Ensure program monitoring and evaluation.

- Annually, each program should review the number of pregnant women found to be HBsAg-positive and the proportion of infants born to HBsAg-positive women who received postexposure prophylaxis within 12 hours of birth, received their third vaccine dose at 6 months of age, and had postvaccination serologic testing.
- Reasons should be determined for a >10% difference between the expected and identified number of HBsAg-positive pregnant women, on-time postexposure prophylaxis rates of <90%, on-time third-dose completion rates of <90%, and postvaccination test rates of <90%.

Vaccination of Pregnant Women

Recommendations

HBV infection in a pregnant woman can result in severe disease for the mother and chronic infection for the newborn. Therefore, pregnant women at high risk for infection (e.g., injection-drug users, women with STDs, women with multiple sex partners) should be vaccinated. If pregnant women receive hepatitis B vaccine during pregnancy, HBsAg testing should be done either before or >21 days after administration of a vaccine dose to avoid transient HBsAg positivity that can be detected in some persons after vaccination.

Universal Vaccination of Infants

Recommendations

1. All infants should receive the hepatitis B vaccine series as part of the recommended childhood immunization schedule. (For recommendations on management of infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status, see: Prevention of perinatal HBV infection.)
2. The first dose of vaccine should be administered soon after birth and before hospital discharge (birth dose). All delivery hospitals should include hepatitis B vaccination as part of standing orders for the routine care of medically stable infants weighing ≥2,000 grams at birth. Only single-antigen hepatitis B vaccine should be used for the birth dose.
3. The first dose can be delayed until after hospital discharge only if there is a physician's order to defer the vaccine based on documentation of a negative maternal HBsAg test result during this pregnancy. A first dose not administered before hospital discharge should be

administered by age 2 months.

4. The vaccine series should be completed according to a recommended schedule with either single-antigen vaccine or a combination vaccine that contains the hepatitis B vaccine antigen (e.g., Hib-hepatitis B, DTaP-IPV-hepatitis B) (**Tables 2 and 4**). When a birth dose is administered, infants may receive a total of four doses of hepatitis B vaccine. The final dose should not be administered before age 24 weeks (164 days).
5. Preterm infants weighing <2,000 grams and born to HBsAg-negative mothers should have their first vaccine dose delayed until they reach a chronological age of 1 month (**Tables 4 and 5**).
6. In populations with currently or previously high rates of childhood HBV infection (i.e., Alaskan Natives, Pacific Islanders, immigrant families from Asia, Africa, and other countries with intermediate or high endemic rates of infection [**Figure 1**]), the first dose of hepatitis B vaccine should be administered at birth and the final dose at age 6-12 months.

Implementation

States are encouraged to adopt regulations or laws that require hepatitis B vaccination for entry into child daycare, kindergarten, and/or elementary school to ensure high vaccine coverage among infants and children.

Vaccination of Children and Adolescents Who Were Not PreviouslyVaccinated

Recommendations

1. Hepatitis B vaccination is recommended for all children and adolescents <19 years of age.

2. Children and adolescents who have not previously received hepatitis B vaccine should be routinely vaccinated at any age with an appropriate dose and schedule (**Tables 2 and 4**).
3. Selection of a vaccine schedule should consider the need to achieve compliance with vaccination and to maximize vaccine coverage.

Implementation

1. Special efforts should be undertaken to ensure high vaccine coverage in the following groups:
   - Children and adolescents who were not previously vaccinated and who reside in a household of a Pacific Islander or first-generation immigrant family from Asia, Africa, or other intermediate- or high-endemic areas (**Figure 1**).
   - Children aged 11-12 years. These children should have a review of their immunization record and should complete the vaccine series if they were not previously vaccinated or were incompletely vaccinated.
   - Older adolescents. Older adolescents should be vaccinated whenever possible in settings that provide healthcare services to this age group, including private medical practices, adolescent clinics, high school and college health clinics, STD clinics, family planning clinics, correctional facilities, drug treatment programs, and programs for high-risk youth.
2. To ensure high vaccination coverage among older children and adolescents, states are encouraged to adopt regulations or laws that require hepatitis B vaccination before entry into middle school or its equivalent. Vaccination requirements should also be considered for older high school students and before college entry, when feasible.

Vaccination of Adults Who Were Not Previously Vaccinated

Recommendations

1. Hepatitis B vaccination is recommended for all adults in the following target groups and for anyone who wants to be protected from HBV infection:

Persons with behavioral risks

- All sexually active heterosexual persons who are not in a long-term, mutually monogamous relationship (e.g., persons who have had more than one sex partner in the previous 6 months)
- All men who have sex with men
- All injection-drug users, including persons who have a history of injection drug use or who are at risk for injection-drug use (e.g., history of incarceration or non-injecting illegal drug use)

Persons with medical conditions

- All persons being screened or ever treated for STDs
- All hemodialysis patients, persons with pre-endstage renal failure not on hemodialysis, peritoneal dialysis patients, and home dialysis patients
- All persons with chronic liver disease, especially persons with risk factors for infection
- All persons with HIV infection

Occupational groups

- All healthcare and public safety workers who are at occupational risk of exposure to blood or blood-contaminated body fluids (e.g., dentists, dental hygienists, emergency medical technicians, first responders, laboratory technologists/technicians, nurses, nursing assistants, nurse practitioners, phlebotomists, physician's assistants, students

entering these professions)

- All staff of correctional faculties
- All staff of institutions for the developmentally disabled

Groups in institutional-, medical-, and custodial-care settings

- All inmates who receive a medical evaluation in federal and state prisons, jails, and juvenile correction facilities
- All residents of institutions for the developmentally disabled

Other groups

- All sexual and household contacts of HBsAg-positive persons, including family members of HBsAg-positive immigrants and international adoptees
- All international travelers to areas with high or intermediate levels of endemic HBV infection (HBsAg prevalence >2%; **Figure 1**) who will have close contact with the local population (i.e., sexual contact or daily physical contact) or who are likely to seek medical, dental, or other treatment in local facilities
- All victims of sexual assault

2. Persons who are not previously vaccinated or immune to HBV infection should be vaccinated using the age-appropriate vaccine dose and schedule **(Tables 2 and 4)**. Selection of a vaccination schedule should consider the need to achieve compliance with vaccination, especially among hard-to-reach populations. In all settings, vaccination should be initiated even though completion of the vaccine series may not be assured.
3. Persons with a history of hepatitis B vaccination should be identified based on reliable vaccination records (e.g., personal, school, physician, immunization registry) (See: Management of persons with unknown or uncertain vaccination status).

4. For some adult risk groups and in some settings, serologic testing to determine prior immunity to infection may be indicated (See: Prevaccination serologic testing for susceptibility).

Implementation

1. Hepatitis B vaccine should be routinely available and offered to unvaccinated adults in the above target groups in settings that provide healthcare services to this age group, including all of the settings listed in **Table 7**.
2. All unvaccinated adults should be offered vaccine when seen in STD clinics, HIV/AIDS testing and counseling programs, clinics for treatment of persons with HIV infection, and substance abuse prevention, treatment, and harm-reduction clinics and programs.
3. In settings where all persons do not need to receive hepatitis B vaccination **(Table 7)**, all patients should be assessed clinically, including taking an appropriate history, to identify those for whom vaccination is indicated. Because it may be difficult in some circumstances to elicit a specific risk factor for infection, healthcare providers should consider their ability to accurately assess risk factors when evaluating indications for hepatitis B vaccination.
4. Programs should be implemented to ensure high hepatitis B vaccine coverage. Programs should include identification of all at-risk persons, tracking of vaccine series completion, and educational efforts to encourage vaccination. Programs should be implemented for:
   - Persons at occupational risk of exposure to blood or blood-contaminated body fluids **(Table 7)**
   - At-risk persons in institutional-, medical-, and custodial-care facilities **(Table 7)**
   - Susceptible household and sex contacts of HBsAg-positive persons (See: Postexposure

prophylaxis to prevent HBV infection) whenever these persons are identified, including in screening programs for blood donors, immigrants (See: Screening and vaccination of immigrants and international adoptees), and pregnant women (See: Prevention of perinatal HBV transmission).

5. When feasible, targeted outreach programs should be implemented to vaccinate at-risk persons who rarely visit traditional healthcare settings and public health programs (e.g., homeless persons, injection-drug users).
6. All settings in which hepatitis B vaccine is provided should:
   - Have vaccination protocols
   - Provide education materials about hepatitis B disease and vaccination
   - Have systems to track vaccine series completion.
7. States are encouraged to implement immunization registries for adolescents and adults to track receipt of hepatitis B vaccine, with particular emphasis on persons who receive vaccine in multiple settings.

Postexposure Prophylaxis to Prevent HBV Infection

This section provides postexposure immunoprophylaxis recommendations for persons with occupational exposure to blood or body fluids that contain blood, for sexual and household contacts of persons with acute hepatitis B and chronic HBV infection, and for victims of sexual assault. Recommendations for postexposure prophylaxis to prevent perinatal HBV infection are provided above (See: Prevention of perinatal HBV transmission *and* Management of pregnant women).

When postexposure prophylaxis is indicated, it should be administered as soon as possible after exposure (preferably within 24 hours, especially for occupational exposures). Hepatitis B vaccine can be administered simultaneously with HBIG, if indicated, at a separate site. If an exposure is identified >14 days after its occurrence, only hepatitis B vaccine should be administered (although the amount of protection afforded is not known).

Persons with occupational exposure to blood or body fluids that contain blood

1. After a percutaneous (needlestick, laceration, bite) or permucosal (ocular, mucous-membrane) exposure to blood or body fluids that contain or might contain HBV, a blood sample should be obtained from the person who was the source of the exposure to determine the HBsAg status of the source.
2. **Table 8** outlines recommendations for prophylaxis after an exposure, according to the HBsAg status of the source and the immunization status (vaccination history, anti-HBs response) of the exposed person.
    - Exposed persons who are in the process of being vaccinated but who have not completed the vaccination series should complete the vaccine series using the age-appropriate vaccine dose and schedule **(See Tables 2 and 4)**, and HBIG should be added as indicated.
    - Exposed persons who are known not to have responded to a primary vaccine series should receive a single dose of HBIG and reinitiate the hepatitis B vaccine series with the first dose of the hepatitis B vaccine as soon as possible after exposure. Alternatively, they should receive two doses of HBIG, one dose as soon as possible after exposure and the second dose 1 month later. The option of administering one dose of HBIG and

reinitiating the vaccine series is preferred for nonresponders who did not complete a second three-dose vaccine series. For persons who previously completed a second vaccine series but failed to respond, two doses of HBIG are preferred.

Sex partners of persons with acute hepatitis B

1. Unvaccinated sex partners of persons with acute hepatitis B should receive a single dose of HBIG (0.06 mL/kg) and the first dose of the hepatitis B vaccine series as soon as possible after exposure, and should complete the series using the age-appropriate vaccine dose and schedule **(See Tables 2 and 4)**.
2. Exposed persons who are in the process of being vaccinated but who have not completed the vaccine series should receive the appropriate dose of HBIG and should complete the vaccine series as scheduled.
3. If feasible, exposed persons who have previously completed the vaccine series should be tested for anti-HBs and provided immunoprophylaxis as indicated in **Table 8**. Alternatively, a single vaccine booster dose may be administered.
4. Testing of sex partners for susceptibility to HBV infection may be considered at the time of administration of the first vaccine dose (See: Prevaccination serologic testing for susceptibility).

Household contacts of persons with acute hepatitis B

1. An unvaccinated infant whose mother or primary caregiver has acute HBV infection should receive a single dose of HBIG (0.5 mL) and the first dose of the hepatitis B vaccine series as

soon as possible, and should complete the series using the age-appropriate vaccine dose and schedule **(See Tables 2 and 4)**.

2. Unvaccinated household contacts with blood exposure from a person with acute hepatitis B (e.g., shared toothbrush or razor) should receive HBIG (0.6 mL/kg) and the first dose of the hepatitis B vaccine series as soon as possible after exposure, and should complete the vaccine series using the age-appropriate vaccine dose and schedule **(See Tables 2 and 4)**.
3. Exposed persons who are in the process of being vaccinated but who have not completed the vaccine series should receive the appropriate dose of HBIG and should complete the vaccine series as scheduled.
4. Vaccination histories should be assessed for all household contacts, and all unvaccinated persons should be vaccinated, if feasible.

Household contacts and sex partners of persons with chronic HBV infection

1. Unvaccinated household contacts and sex partners of chronically infected persons should receive the first dose of hepatitis B vaccine at the time of their initial clinical evaluation and should complete the vaccine series using the age-appropriate vaccine dose and schedule **(See Tables 2 and 4)**.
2. Household contacts with written documentation of full vaccination should be considered protected and need no further vaccine doses. Persons who are not fully vaccinated should complete the vaccine series.
3. Sex partners of chronically infected persons should be counseled to use methods (e.g., abstinence, condoms) to protect themselves from sexual HBV transmission unless they have been demonstrated to be immune (anti-HBs ≥10 mIU/mL) after vaccination **(**See:

Postvaccination testing for serologic response**)**, or previously infected (anti-HBc positive).

4. Testing of unvaccinated persons for susceptibility to HBV infection may be considered at the time of administration of the first vaccine dose (See: Prevaccination serologic testing for susceptibility).

Victims of sexual assault or sexual abuse

1. If the HBV-infection status of the perpetrator is unknown, unvaccinated victims of sexual assault or sexual abuse should receive the first dose of hepatitis B vaccine at the time of the initial clinical evaluation and should complete the vaccine series using the age-appropriate vaccine dose and schedule **(See Tables 2 and 4)**. Victims who have written documentation of full vaccination should be considered protected and need no further treatment. Persons who are not fully vaccinated should complete the vaccine series.
2. If the perpetrator is known to be HBsAg-positive, the victim should be managed as a sex partner of a person with acute hepatitis B (See: Sex partners of persons with acute hepatitis B*)*.

Vaccination Management Issues

Prevaccination serologic testing for susceptibility

1. Serologic testing to determine susceptibility prior to vaccination is not necessary and is recommended only in certain circumstances. Vaccination of persons who are immune to HBV infection because of current or prior infection or vaccination does not increase the risk for adverse events.

2. Because of the low prevalence of HBV infection among infants, children, and adolescents, testing is not indicated for these age groups, except for immigrants and international adoptees (See: Screening and vaccination of immigrants and international adoptees).
3. Prevaccination testing may be considered to reduce the cost of vaccinating adult populations that have an expected high prevalence of HBV infection. The decision to test should be based on a) the expected prevalence of HBV infection, b) the cost of vaccination compared with the cost of serologic testing (including the cost of an additional visit, if required), and c) the likelihood that testing will not interfere with completion of the vaccine series. Testing is likely to be cost-effective in adult populations with a prevalence of HBV infection of >20%-30%.
4. Anti-HBc is the test of choice in settings that provide care to persons with a high prevalence of natural HBV infection.
5. Persons who are anti-HBc positive should be tested for HBsAg. If found to be HBsAg negative, no further action is required. If found to be HBsAg positive, the person should receive appropriate medical follow-up, including counseling and evaluation for antiviral treatment (**Appendix A**), and susceptible household and sex contacts should be vaccinated (See: Postexposure prophylaxis to prevent HBV infection).
6. When completion of the vaccine series cannot be ensured, the first vaccine dose should be administered at the time of collection of the blood sample for serologic testing.

Postvaccination testing for serologic response

1. Serologic testing for immunity after vaccination is recommended only for persons whose subsequent clinical management depends on knowledge of their immune status. Testing is not necessary after routine vaccination of infants, children, adolescents, or adults.

2. Postvaccination testing is recommended for the following persons:
   - Healthcare and public safety workers at high risk of continued percutaneous or permucosal exposure to blood or body fluids (e.g., dentists, dental hygienists, emergency medical technicians, first responders, laboratory technologists/technicians, nurses, nurse practitioners, phlebotomists, physicians, physicians' assistants, students entering these professions), to determine the need for revaccination and to guide postexposure prophylaxis. Testing of persons at low risk of continued permucosal or percutaneous exposure to blood or body fluids (e.g., public safety workers, healthcare workers without direct patient contact) is not necessary.
   - Infants born to HBsAg-positive women, to determine the success of prophylaxis and the need for revaccination or follow-up
   - Chronic hemodialysis patients, HIV-infected persons, and other immunocompromised persons (e.g., hematopoietic stem cell transplant recipients), to determine the need for revaccination and the type of follow-up testing
   - Sex partners of HBsAg-positive persons, to determine the need for revaccination and the need for other means to protect themselves from HBV infection
3. Testing should be performed 1-2 months after administration of the last dose of the vaccine series (except for infants of HBsAg-positive mothers; see: Prevention of perinatal HBV infection and management of pregnant women).
4. Testing should be done using a method that allows determination of a protective level of anti-HBs (≥10 mIU/mL).
5. Persons found to have anti-HBs levels of <10mIU/mL after the primary vaccine series should be revaccinated (See: Management of primary nonresponders).

Assessing immunity in persons with a reliable vaccination history

1. A reliable vaccination history is defined as a written, dated record (personal, school, physician, immunization registry) of each dose of a complete series. Healthcare and public safety workers who have written documentation of a complete vaccine series but who have never had postvaccination testing do not need serologic testing for anti-HBs unless they have a percutaneous or permucosal exposure to blood or body fluids.
2. Some schools for healthcare professionals have policies that require serologic documentation of immunity to HBV infection before students start clinical rotations, even if they have written documentation of a complete vaccine series. If anti-HBs testing is performed and anti-HBs levels are <10 mIU/mL, evidence of immune memory can be determined by administering a single dose of vaccine and retesting for anti-HBs in 1-2 months. Persons with anti-HBs <10 mIU/mL after a single booster dose should be considered susceptible and should receive two additional vaccine doses using the age-appropriate vaccine dose and schedule **(Tables 2 and 4)**; these persons should be retested 1-2 months after the last dose.

Unknown or uncertain vaccination status

Vaccination providers frequently encounter persons who lack documentation of hepatitis B vaccination.

1. In most clinical practice settings and in situations where postexposure prophylaxis is indicated (See: Postexposure prophylaxis to prevent HBV infection), providers should accept only written, dated records (e.g., personal, school, physician, immunization registry) as evidence of vaccination. Although vaccinations should not be postponed if records cannot be found, an attempt to locate missing records should be made by contacting previous healthcare providers and searching for personally held records. Persons whose records

cannot be located should be considered susceptible and started on the age-appropriate vaccine schedule.

2. Serologic testing for anti-HBs may be considered as an alternative to initiation of vaccination for persons who are likely to have been vaccinated but who lack a reliable vaccination history. When testing is performed, the three-dose vaccine series should be administered to persons with anti-HBs levels <10 mIU/mL.

Interrupted vaccine schedules

1. In any age group, when the hepatitis B vaccine schedule is interrupted, the vaccine series does not need to be restarted.
2. If the series is interrupted after the first dose, the second dose should be given as soon as possible, and the second and third doses should be separated by an interval of at least 8 weeks.
3. If only the third dose is delayed, it should be administered as soon as possible.
4. It is not necessary to restart the vaccine series for infants switched from one vaccine brand to another.

Management of primary nonresponders

1. Revaccination is recommended for persons, including infants born to HBsAg-positive women, who do not respond to a primary three-dose series of hepatitis B vaccine as determined by appropriate postvaccination testing for anti-HBs (See: Postvaccination testing for serologic response). Administration of three doses on an appropriate schedule (**Table 4**),

followed by serologic testing 1-2 months after the third dose, is usually more practical than serologic testing after one or more doses of vaccine.

2. Nonresponders should be tested for HBsAg. Persons found to be HBsAg-positive should be provided with appropriate medical management, counseling, and vaccination of household and sexual contacts (**Appendix A**).
3. Nonresponders who are HBsAg-negative should be considered susceptible to HBV infection and should be counseled about precautions to prevent HBV infection and the need to obtain HBIG postexposure prophylaxis for any known or likely parenteral exposure to HBsAg-positive blood (See: Postexposure prophylaxis to prevent HBV infection).

Minimum dosing intervals and management of persons who were incorrectly vaccinated

1. For all age groups, the minimum recommended dosing intervals are 4 weeks between the first and second doses and 8 weeks between the second and third doses. In infants, administration of the final dose is not recommended before age 24 weeks (164 days). In older age groups, the minimum interval between the first and third doses is 16 weeks.
2. Inadequate doses of hepatitis B vaccine (**Table 2**) or doses received after a shorter-than-recommended dosing interval should be readministered.

Screening and vaccination of immigrants and international adoptees

1. Persons who reside in the United States but were vaccinated in other countries should be considered fully vaccinated if they have written documentation of at least three doses of vaccine with recommended minimum intervals, including the third dose at ≥24 weeks of age. If they were not vaccinated according to recommended minimum intervals, they should be

revaccinated (See: Minimum dosing intervals and management of persons who were incorrectly vaccinated). Persons without written documentation of full vaccination should complete the vaccine series.

2. All first-generation immigrants (i.e., foreign-born) from Asia, Africa, and other intermediate- and high-endemic countries (**Figure 1),** including international adoptees, should be tested for HBsAg even if they have a history of vaccination. In addition, all unvaccinated second-generation immigrants from these countries (i.e., person with at least one foreign-born parent) should be screened for HBsAg. If found to be HBsAg-negative, no further action is required. If found to be HBsAg positive, the person should receive appropriate medical follow-up, including counseling and evaluation for antiviral treatment (**Appendix A**), and susceptible household and sexual contacts should be vaccinated (See: Postexposure prophylaxis to prevent HBV infection).

Accelerated vaccine schedules

The FDA has not approved accelerated schedules in which hepatitis B vaccine is administered more than once in a month. If clinicians choose to use an accelerated schedule (i.e., doses at days 0, 7, and 14) for travelers who will depart before an approved vaccine schedule can be completed, the person should also receive a booster dose at least 6 months after the start of the series to promote long-term immunity.

Booster doses

1. Booster doses are not recommended for persons with normal immune status who were vaccinated as infants, children, adolescents, or adults. Serologic testing is not recommended

to assess antibody levels in any age group, except in certain circumstances (See: Postvaccination testing for serologic response).

2. For hemodialysis patients, the need for booster doses should be assessed by annual anti-HBs testing. A booster dose should be given when anti-HBs levels decline to <10 mIU/mL.
3. For HIV-infected persons and other immunocompromised persons (e.g., hematopoietic stem cell transplant recipients) the need for booster doses has not been determined. Annual anti-HBs testing and booster doses when anti-HBs levels decline to <10 mIU/mL should be considered in persons with an ongoing high risk of exposure.

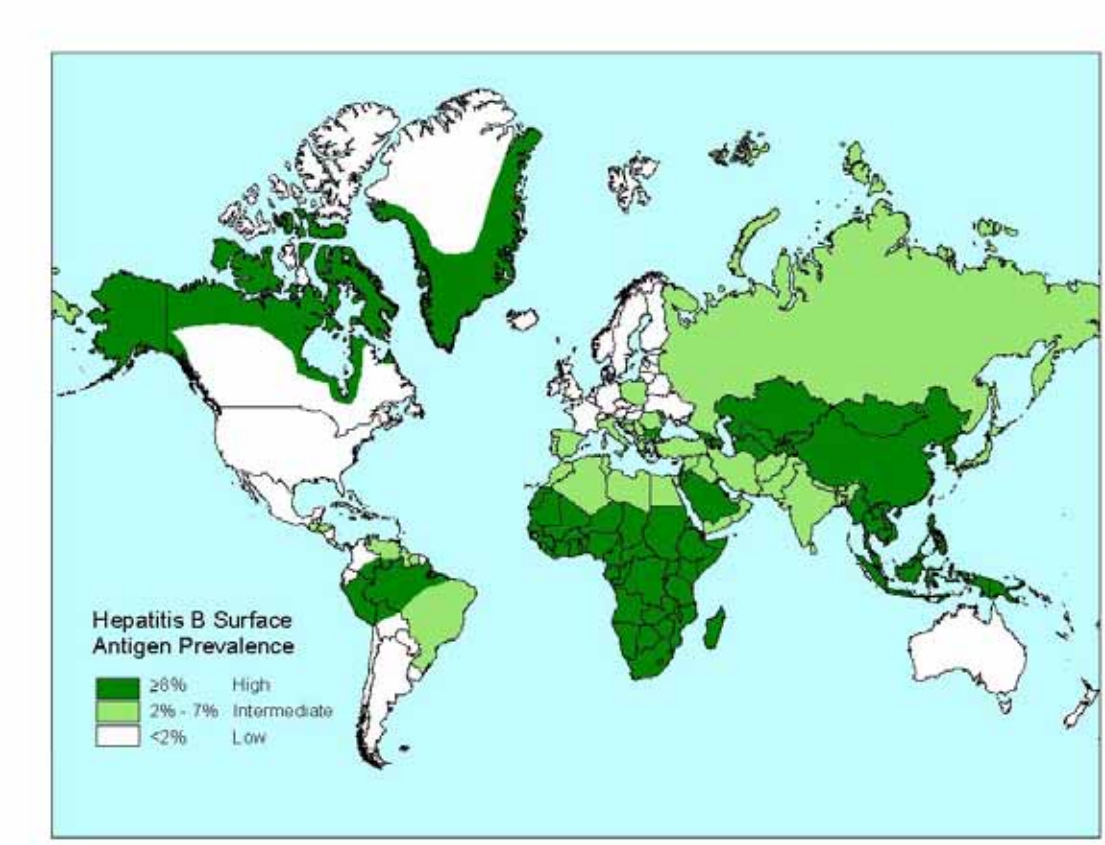

Figure 1. Geographic distribution of chronic HBV infection prevalence

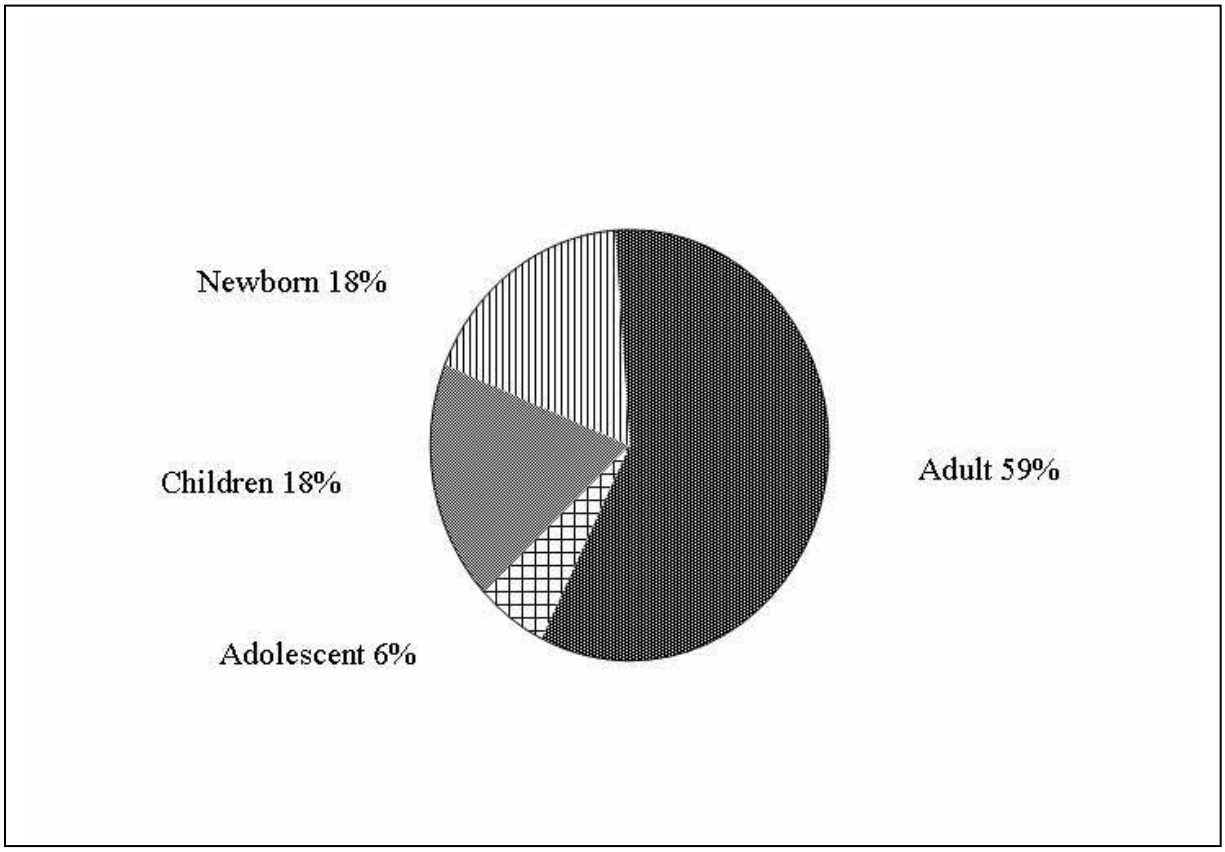

Figure 2. Estimated age at infection of persons with chronic HBV infection before implementation of hepatitis B immunization, United States

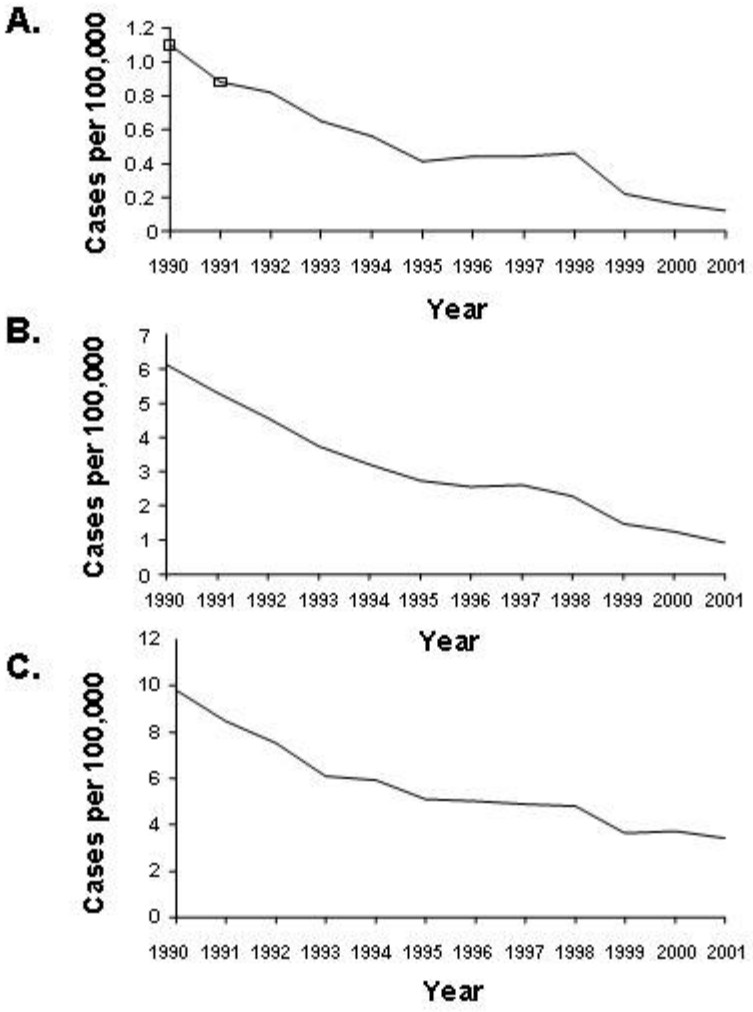

Figure 3. Acute hepatitis B incidence per 100,000, by age group: United States, 1990-2001. A. Children ≤ 11 years of age; B. Adolescents 12-19 years of age; C. Adults ≥ 20 years of age.

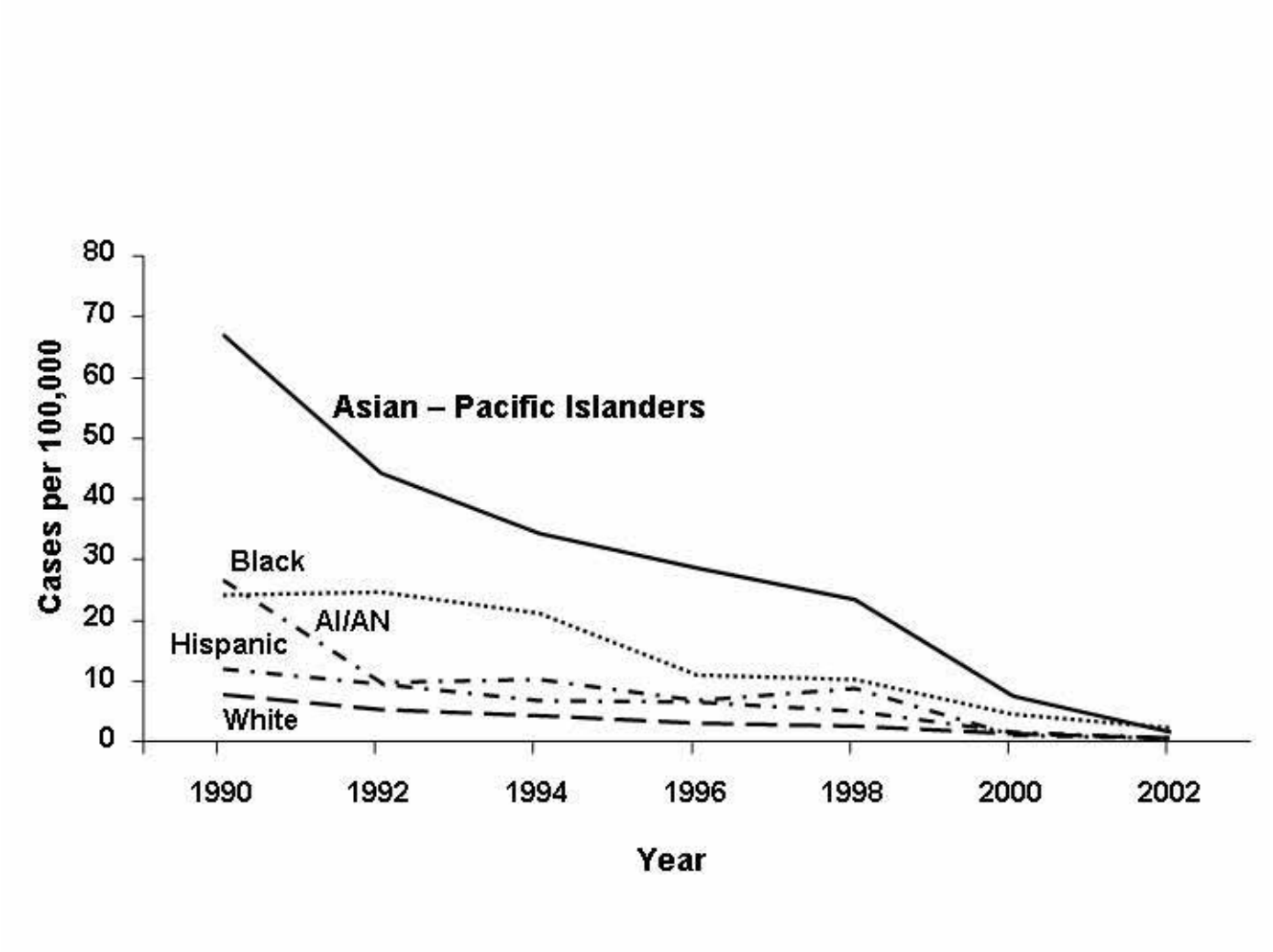

Figure 4. Acute hepatitis B incidence per 100,000 in persons aged <19 years, by race and year: United States, 1990–2002

Table 1. Interpretation of serologic test results for HBV infection

Serologic markers				Interpretation
HBsAg[1]	**Total Anti-HBc[2]**	**IgM[3] Anti-HBc**	**Anti-HBs[4]**	
--	--	--	--	Susceptible; never infected
+	--	--	--	Early acute infection; transient (21days) after vaccination
+	+	+	--	Acute infection
--	+	+	--	Acute resolving infection
--	+	--	+	Past infection; recovered and immune
+	+	--	--	Chronic infection
--	+	--	--	False positive (i.e., susceptible); past infection; or "low-level" chronic infection[5]
--	--	--	+	Immune if titer is ≥10 mIU/mL[6]

[1] Hepatitis B surface antigen; all HBsAg-positive persons are potentially infectious.
[2] Antibody to hepatitis B core antigen
[3] Immunoglobulin M
[4] Antibody to hepatitis B surface antigen
[5] Persons positive for anti-HBc alone are unlikely to be infectious except under unusual circumstances involving direct percutaneous exposure to large quantities of blood (e.g., blood transfusion).
[6] Milli-international units per milliliter

Table 2. Recommended doses of currently licensed formulations of hepatitis B vaccine[1]

Group	Single-antigen vaccines				Combination vaccines					
	RECOMBIVAX HB		ENGERIX-B		COMVAX		PEDIARIX		TWINRIX	
	Dose (µg)[2]	Volume (mL)	Dose (µg)[2]	Volume (mL)	Dose (µg)[2,3]	Volume (mL)	Dose (µg)[2, 4]	Volume (mL)	Dose (µg)[2, 5]	Volume (mL)
Infants										
Mother HBsAg-negative	5[§§]	0.5	10[§§]	0.5	5	0.5	10	0.5	NA	NA
Mother HBsAg-positive	5[6]	0.5	10[6]	0.5	5	0.5	10	0.5	NA	NA
Children (1 - 10 years)	5[6]	0.5	10[6]	0.5	NA	NA	NA	NA	NA	NA
Adolescents							NA	NA	NA	NA
11 - 19 years	5[6]	0.5	10[6]	0.5	NA	NA	NA	NA	NA	NA
11 - 15 years	10[7, 8]	1.0	NA	NA	NA	NA	NA	NA	NA	NA
Adults (≥20 years)	10[7]	1.0	20[7]	1.0	NA	NA	NA	NA	20[9]	1.0[9]
Adult hemodialysis patients and predialysis patients	40[10]	1.0	40[7]	2.0[11]	NA	NA	NA	NA	NA	NA

[1] Hepatitis B vaccines are administered by intramuscular injection in a three-dose series, except where noted, and may be given at the same time as other vaccines. Single-antigen vaccines may be administered with HBIG, but in a separate injection site.
[2] Recombinant HBsAg protein concentration
[3] COMVAX also contains 7.5µg *Haemophilus influenzae* type B polyribosylribitol phosphate (PRP) and 125µg *Neisseria meningitidis* outer membrane protein complex (OMPC).
[4] Pediarix also contains 25 Lf diphtheria toxoid, 10 Lf tetanus toxoid, 25 mcg inactivated pertussis toxin, 25 mcg filamentous hemagglutinin, 8 mcg pertactin, 40 D-antigen Units (DU) Type 1 poliovirus, 8 DU Type 2 poliovirus, and 32 DU Type 3 poliovirus.
[5] Twinrix also contains 720 ELISA Units (EL.U) inactivated hepatitis A virus.
[6] Pediatric formulation
[7] Adult formulation
[8] Given on a two-dose schedule
[9] For persons ≥18 years of age at increased risk of both hepatitis B virus and hepatitis A virus infection.
[10] Dialysis form
[11] Two 1.0-mL 20µg doses given in one site in a four-dose schedule at 0, 1, 2, 6 months.

Table 3. Studies of long-term protection after hepatitis B immunization among persons who responded to a primary vaccine series[1]

Study population and location	No. persons tested	Follow-up, years	Anti-HBs loss, %	HBV infections	
				All no. (%)	Chronic no. (%)
Infants of HBsAg/HBeAg-positive mother					
Taiwan (Wu)	805	10	15	113 (14)	3 (0.4)
Taiwan (Lu)	78	15	30	26 (33)	1 (1.3)
Thailand (Pooverawan)	177	8	10	20 (11)	0 (0)
United States (Stevens)	104	4-9	4	7 (6.7)	0 (0)
United States (Peterson)	16	12	69	0 (0)	0 (0)
Infants and children					
China (Yuen)	148	12	26	2 (1.4)	0 (0)
China (Yuen)	30	18	27	1 (3)	0 (0)
Gambia (Whittle)	63	14	36	14 (22)	0 (0)
United States (Peterson)	17	12.5	76	0 (0)	0 (0)
United States (Watson)	18	13	17	0 (0)	0 (0)
United States – Alaska Natives (Wainwright)	600	10	17	4 (0.7)	0 (0)
Adolescents and Adults					
United States - MSM (Stevens)	127	10	5	5 (4)	0 (0)
United States – Alaska Natives (Wainwright)	272	10	38	6 (2)	0 (0)

United States – MSM (Hadler)	634	7-9	54	48 (8)	0 (0)
Italy – HCWs (Floreani)	310	10	15	0 (0)	0 (0)

[1] Vaccinated persons known to have responded with protective antibody levels following immunization

Table 4. Recommended hepatitis B vaccine schedules

Infant born to HBsAg-negative mother[1]

Single-antigen vaccine[2]		Birth dose[2] + combination[3]		Combination[3] without birth dose[4]	
Dose	**Age**	**Dose**	**Age**	**Dose**	**Age**
1[4]	Birth (before discharge)[5]	1[4]	Birth (before discharge)[5]	1[3]	2 months[5]
2	1 – 4 months	2[3]	2 months	2[3]	4 months
3[6]	6 – 18 months	3[3]	4 months	3[3],[6]	6 months (PEDIARIX) or 12-15 months (COMVAX)
		4[3],[6]	6 months (PEDIARIX) or 12-15 months (COMVAX)		

[1] See **Table 5** for vaccine schedules for preterm infants. Infants in populations with current or previously high rates of childhood infections (i.e., Alaskan Natives; Pacific Islanders; immigrant families from Asia, Africa, and other countries with intermediate or high endemic rates of infection [**Figure 1**]) should begin the vaccine series at birth and complete the series no later than 12 months of age.

[2] Pediatric formulation of either RECOMBIVAX HB or ENGERIX-B

[3] COMVAX (combined hepatitis B-Hib conjugate vaccine) and PEDIARIX (combined hepatitis B-DTaP-IPV vaccine) cannot be administered at birth or before 6 weeks of age.

[4] Pediatric formulation of either RECOMBIVAX HB or ENGERIX-B can be used beginning at birth.

[5] The first dose can be delayed until after hospital discharge only if there is a physician's order to defer the vaccine at birth based on specific documentation of a negative HBsAg test during this pregnancy. If the first dose is not administered before hospital discharge, it should be administered by age 2 months.

[6] The last dose should not be administered before age 24 weeks (164 days).

Table 4 (cont.)

Infant born to HBsAg-positive mother[1]

Single-antigen vaccine[2]		**Single-antigen**[2] **+ combination vaccine**[3]	
Dose	**Age**	**Dose**	**Age**
1[4]	Birth (within 12 hours)	1 [3, 4]	Birth (within 12 hours)
HBIG[5]	Birth (within 12 hours)	HBIG[5]	Birth (within 12 hours)
2	1 - 2 months	2[6]	2 months
3	6 months[7]	3[6]	4 months
		4[6]	6 months (PEDIARIX)[7] or 12-15 months (COMVAX)

1 See **Table 5** for vaccine schedules for preterm infants.
2 Pediatric formulation of either RECOMBIVAX HB or ENGERIX-B
3 COMVAX (combined hepatitis B-Hib conjugate vaccine) and PEDIARIX (combined hepatitis B-DTaP-IPV vaccine) cannot be administered at birth or before 6 weeks of age.
4 Pediatric formulation of either RECOMBIVAX HB or ENGERIX-B can be used beginning at birth.
5 Hepatitis B immune globulin (0.5 mL) given intramuscularly in a separate site from vaccine
6 PEDIARIX administered at 2, 4, 6 months of age to complete immunization against hepatitis B and primary immunization against diphtheria, tetanus, pertussis, and polio. COMVAX administered at 2, 4, and 12-15 months of age to complete immunization against both hepatitis B and *Haemophilus influenzae* type b.
7 The last dose in the vaccine series should not be administered before age 24 weeks (164 days).

Table 4 (cont.)

Infant born to mother not tested for HBsAg[1, 2]

Single-antigen vaccine[3]		**Single-antigen**[3] **+ combination vaccine**[4]	
Dose	**Age**	**Dose**	**Age**
1[5]	Birth (within 12 hours)	1[5]	Birth (within 12 hours)
2	1 - 2 months	2[6]	2 months
3	6 months[7]	3[6]	4 months
		4[6]	6 months (PEDIARIX)[7] or 12-15 months (COMVAX)

1 See **Table 5** for schedules for preterm infants.

2 Mother should have blood drawn and tested for HBsAg as soon as possible after admission for delivery.

3 Pediatric formulation of either RECOMBIVAX HB or ENGERIX-B.

4 COMVAX (combined hepatitis B-Hib conjugate vaccine) and PEDIARIX (combined hepatitis B-DTaP-IPV vaccine) cannot be administered at birth or before 6 weeks of age.

5 If the mother is found to be HBsAg positive, the infant should receive HBIG (0.5 mL) as soon as possible and up to 7 days of age.

6 PEDIARIX administered at 2, 4, 6 months of age to complete immunization against hepatitis B and primary immunization against diphtheria, tetanus, pertussis and polio. COMVAX administered at 2, 4, and 12-15 months of age to complete immunization against both hepatitis B and *Haemophilus influenzae* type b.

7 The last dose in the vaccine series should not be administered before age 24 weeks (164 days).

Table 4 (cont.)

Children (1-10 years)

This age group can be vaccinated according to any of the following schedules:

- 0, 1, 6 months
- 0, 2, 4 months

Selection of a vaccine schedule should consider the need to optimize compliance with vaccination.

Adolescents (11-19 years)

This age group can be vaccinated according to any of the following schedules:

- 0, 1, 6 months
- 0, 1, 4 months
- 0, 2, 4 months
- 0, 12, 24 months

The two-dose schedule of RECOMBIVAX HB (adult) for adolescents 11-15 years of age should be administered at 0 and 4-6 months. Adolescents who are older than 15 years of age when scheduled to receive the second dose should be switched to a three-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.

Selection of a vaccine schedule should consider the need to optimize compliance with vaccination.

Adults

This age group can be vaccinated according to any of the following schedules:

- 0, 1, 6 months
- 0, 1, 4 months
- 0, 2, 4 months
- 0, 1, 2, 12 months (for persons, such as travelers, who require rapid protection)

TWINRIX should be administered at 0, 1, 6 months.

Table 5. Hepatitis B immunization management of premature infants weighing <2,000 grams

Maternal HBsAg status	Infant weighing <2,000 grams
Positive	HBIG + hepatitis B vaccine (within 12 hrs of birth) Restart vaccine series beginning at 1 month of age (see **Table 4**). *DO NOT count birth dose as part of the vaccine series.* Test for HBsAg and anti-HBs at 9-15 months of age, or 1-2 months after last dose if administered after 8 months of age.
Unknown	HBIG + hepatitis B vaccine (within 12 hrs of birth) Test mother for HBsAg. Restart vaccine series according to recommended schedule based on the mother's HBsAg result (see **Table 4**). *DO NOT count birth dose as part of the vaccine series.*
Negative	Delay first dose of hepatitis B vaccine until 1 month of age, or hospital discharge. Complete the vaccine series (see **Table 4**).

Table 6. Estimated expected births to HBsAg-positive women: United States, 2002

Maternal race/ethnicity	2002 births	Estimated maternal HBsAg prevalence	Estimated births to HBsAg-positive women
White, non-Hispanic	2,298,156	0.13	2,988
African-American	593,691	0.5	2,968
Asian/Pacific Islander			
Foreign born	175,264	8.9	15,598
U.S. born	35,643	1.4	499
Hispanic	876,642	0.09	789
Other	42,330	0.5	212
Total	4,021,726		23,054

Table 7. Settings where hepatitis B vaccine should be routinely available and offered

Setting	Offer hepatitis B vaccine to:	Comments
Clinical Care		
STD clinics	All patients	
HIV/AIDS testing and counseling programs	All patients	
Clinics for treatment of persons with HIV infection	All patients	•Vaccinated patients who are immunocompromised should be tested annually for anti-HBs. •A booster vaccine dose should be given when anti-HBs level declines to <10mIU/mL.
Substance abuse prevention, treatment, and harm-reduction clinics and programs (including needle-exchange programs)	All patients	
Community health centers	All patients in target groups **(See Vaccination of Adults)**	All patients should be assessed to identify persons in risk groups
Family planning clinics	All patients in target groups (**See Vaccination of Adults**)	All patients should be assessed to identify persons in risk groups
Primary care and specialty offices	All patients in target groups **(See Vaccination of Adults)**	All patients should be assessed to identify persons in target groups
International travel clinics	Travelers to areas with high or intermediate levels of endemic HBV infection (HBsAg prevalence >2%; Figure 2) who will have close contact with the local population (i.e., sexual contact or daily physical contact) or who are likely to seek medical, dental, or other treatment in local facilities	
Emergency rooms	•Victims of sexual assault •Household and sexual contacts of persons with acute hepatitis B •Persons exposed to HBV-contaminiated blood or body fluids	
Institutional, Medical, and Custodial Care		
Correctional facilities (e.g., prisons, jails, juvenile detention centers)	•All inmates who receive a medical evaluation •All unvaccinated inmates, if feasible	Hepatitis B vaccine series should be initiated regardless of the expected length of stay in the facility.

Dialysis facilities	All hemodialysis patients, patients with pre-endstage renal failure, peritoneal dialysis patients, home dialysis patients	•Vaccinated patients on hemodialysis should be tested annually for anti-HBs. •A booster vaccine dose should be given when anti-HBs level declines to <10mIU/mL.
Institutions for the developmentally disabled	All residents	Unvaccinated residents should be vaccinated at the time of admission to the facility.
Nonresidential daycare facilities for the developmentally disabled (e.g., schools, sheltered workshops)	Classmates/attendees in settings where an HBsAg-positive client behaves aggressively or has special medical problems	
Occupational Health		
Correctional facilities (e.g., prisons, jails, juvenile detention centers)	All staff with risk of percutaneous or permucosal exposure to blood or body fluids	
Dialysis clinics	All staff with risk of percutaneous or permucosal exposure to blood or body fluids	
First-responder programs	All staff with risk of percutaneous or permucosal exposure to blood or body fluids	
Healthcare facilities	All staff with risk of percutaneous or permucosal exposure to blood or body fluids	
Institutions for the developmentally disabled	All staff with a risk of percutaneous or permucosal exposure to blood or body fluids	
Long-term care facilities (e.g., nursing homes)	All staff with a risk of percutaneous or permucosal exposure to blood or body fluids	
Nonresidential daycare programs for the developmentally disabled (e.g., schools, sheltered workshops)	Staff in settings attended by developmentally disabled persons known to be HBsAg positive	

Table 8. Recommendations for postexposure prophylaxis after percutaneous or permucosal exposure to HBV

	Treatment			
Vaccination and antibody status of exposed person[1]	**Source HBsAg-positive**	**Source HBsAg-negative**	**Source unknown or not tested**	
			High risk	**Low risk**
Unvaccinated	HBIG[2] (1 dose) and begin hepatitis B vaccine series	Begin hepatitis B vaccine series	Begin hepatitis B vaccine series	Begin hepatitis B vaccine series
Previously vaccinated				
Known responder[3]	No treatment	No treatment	No treatment	No treatment
Nonresponder[3]				
Not revaccinated[4]	HBIG (1dose) and begin a revaccination series	No treatment; begin a revaccination series	HBIG (1 dose) and begin a revaccination series	Begin a revaccination series
After revaccination[4]	HBIG (2 doses)[5]	No treatment	HBIG (2 doses)[5]	No treatment
Antibody response unknown	Test for anti-HBs If adequate,[3] no treatment If inadequate, HBIG x 1 and vaccine booster	No treatment	Test for anti-HBs If adequate,[3] no treatment If inadequate, give vaccine booster and check anti-HBs in 1-2 months	

1 Persons known to have been infected with HBV are immune and require no treatment.
2 Hepatitis B immune globulin (0.06 ml/kg) administered intramuscularly.
3 Adequate response is anti-HBs ≥10 mIU/mL after vaccination.
4 Revaccination = additional three-dose series of hepatitis B vaccine administered after the primary series.
5 First dose as soon as possible after exposure and the second 1 month later.

APPENDIX A

Management of HBsAg-Positive Persons

This section provides recommendations for management of all HBsAg-positive persons. Additional recommendations for management of HBsAg-positive persons who are coinfected with HIV are available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5315a1.htm

1. HBsAg-positive persons should be retested to verify the presence of HBsAg. Patients found to be HBsAg-negative most likely had a transient acute infection. Patients found to be HBsAg-positive should be tested for IgM anti-HBc to distinguish between acute and chronic infection. The presence of IgM anti-HBc usually indicates acute hepatitis B. The absence of IgM anti-HBc and/or the persistence of HBsAg for 6 months indicate chronic HBV infection.
2. All patients with chronic HBV infection should be monitored every 6-12 months for liver disease and hepatocellular carcinoma (HCC). The evaluation should include:
   - Medical history
   - Physical examination for clinical evidence of liver disease (e.g, jaundice, ascites, variceal hemorrhage)
   - Laboratory tests to assess serologic and virologic markers of HBV infection, such as HBsAg, anti-HBs, HBeAg, anti-HBe, and HBV DNA.
   - Laboratory tests to assess biochemical markers of liver disease, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, albumin, platelet count, and prothrombin time.
   - Tests to screen for HCC (e.g., alfa-fetoprotein, ultrasound), especially if the patient is in a high-risk group (i.e., age >45 years, cirrhosis, or a family history of HCC).
3. Persons with chronic HBV infection should be referred for further assessment to a physician experienced in the management of chronic liver disease. Early intervention with antiviral treatment may benefit patients with signs of active liver disease.
4. Sex partners and household contacts of chronically infected persons should be identified. Unvaccinated sex partners and household contacts should receive the first dose of

hepatitis B vaccine at the time of their initial clinical evaluation and should complete the vaccine series. Persons who are not fully vaccinated should complete the vaccine series. Testing of sex partners and household contacts for susceptibility to HBV infection may be considered at the time of administration of the first vaccine dose (See: Prevaccination serologic testing for susceptibility).

5. Sex partners of chronically infected persons should be counseled to use methods (e.g., abstinence, condoms) to protect themselves from sexual HBV transmission unless they have been demonstrated to be immune (anti-HBs ≥10 mIU/mL) after vaccination **(**See: Postvaccination testing for serologic response**)**, or previously infected (anti-HBc positive).
6. To reduce the risk for transmission to others, chronically infected persons should be advised:
   - About the risk of household, sexual, and needle-sharing transmission and the need for such contacts to receive hepatitis B vaccine
   - To use methods (e.g., abstinence, condoms) to protect non-immune sex partners from sexual HBV transmission
   - To cover cuts and skin lesions to prevent the spread of infectious secretions or blood
   - not to donate blood, plasma, body organs, other tissue, or semen
   - Not to share household articles such as toothbrushes and razors that could become contaminated with blood
7. To protect the liver from further harm, HBsAg-positive persons should be advised to:
   - Avoid or limit alcohol consumption because of the effects of alcohol on the liver
   - Not start any new medicines, including over-the-counter and herbal medicines, without checking with their doctor
   - Obtain vaccination against hepatitis A if liver disease is found to be present
8. When seeking medical or dental care, HBsAg-positive persons should be advised to inform those responsible for their care of their HBsAg status so that they can be appropriately evaluated and managed.
9. Infants born to HBsAg-positive women should be given hepatitis B immunization beginning at birth to prevent perinatal HBV infection (See: Prevention of perinatal HBV infection*)*.

10. Other counseling messages:

- HBV is not spread by hugging, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact.
- Persons should not be excluded from work, school, play, child-care or other settings because they are infected with HBV.
- Involvement with a support group might help patients cope with chronic HBV infection.